2.4.5 Cancer of the colorectum

The Working Group examined data from 41 occupational cohorts and 13 case–control studies that reported data on associations between asbestos exposure and cancer of the colon and rectum (See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.7.pdf). The Working Group made the decision to combine information on these two sites, although a few comments in several places in the text about the two sites considered separately have also been made.

(a) Cohort studies

An association between occupational exposure to asbestos and cancer of the colorectum was first reported in 1964 by Selikoff *et al.* in a cohort of 632 male insulation workers in New York and New Jersey, USA (Selikoff *et al.*, 1964). Further analysis of this cohort found a positive relationship between duration of work with asbestos and risk of cancer of the colorectum, in that the SMR increased from 0.00 (95%CI: 0.00–18.45) in workers with < 20 years exposure, to 3.68 (95%CI: 1.48–7.59) among workers with 20–35 years' exposure, and to 2.58 (95%CI: 1.48–4.19) among workers with the longest duration of exposure, > 35 years (Selikoff & Hammond, 1979).

Selikoff *et al.* (1967), in a second report, found an association between occupational exposure to asbestos and cancer of the colorectum in a population of 17800 asbestos insulators across the USA and Canada (SMR, 1.37; 95%CI: 1.14–1.64).

Seidman *et al.* (1986) reported an elevated mortality from cancer of the colorectum in a population of 820 male factory workers in Paterson, NJ, USA, exposed to amosite asbestos (SMR, 2.77; 95%CI: 1.16–2.80). They noted that cancer of the colorectum in asbestos workers tended to be a disease of long latency; they reported that the ratio of observed to expected deaths increased with increasing interval since initial exposure to asbestos.

McDonald *et al.* (1980) reported an overall SMR for cancer of the colorectum of only 0.78 in a study of 10939 men and 440 women workers employed as asbestos miners and millers in Quebec with predominant exposure to chrysotile asbestos. Additionally, however, McDonald *et al.* reported a "clear trend for SMRs to be higher, the heavier the exposure." Thus with increasing levels of cumulative occupational exposure to asbestos dust, relative risks for cancer of the colorectum increased in this cohort from 1.00 in workers with less than 30 mpcf–y cumulative exposure, to 0.93 in workers with 30–300 mpcf–y, to 1.96 in workers with 300–1000 mpcf–y, and then in the group with heaviest exposure, > 1000 mpcf–y, to 5.26.

Albin *et al.* (1990) found an overall SMR for cancer of the colorectum of only 1.5 (95%CI: 0.7–3.0) in a cohort of 1465 asbestos-cement workers in Sweden. A positive association between asbestos exposure and cancer of the colorectum was reported, but when cancer of the colorectum mortality was examined by individual cumulative exposure to asbestos, measured as fibre–years/mL, the SMR was 1.3 (95%CI: 0.5–2.9) for those workers with cumulative exposure of < 15 fibre–years/mL; for those with cumulative exposure of 15–39 fibre–years/mL, the SMR was 1.1(95%CI: 0.3–3.9); and for those workers in highest exposure category with > 40 fibre–years/mL, the SMR for cancer of the colorectum was 3.4 (95%CI: 1.2–9.5). Diagnosis in all but one of the cancers in the highest exposure category was verified by pathological review, and no case of certified or probable mesothelioma was found. The trend towards increasing mortality from cancer of the colorectum with increasing cumulative exposure to asbestos was statistically significant ($P = 0.04$). A similar trend was seen for cancer of the colorectum morbidity.

Excess mortality from colon cancer was observed in a heavily exposed cohort of over

5000 workers in the east end of London, who had produced asbestos insulation board and were followed for 30+ years (Berry *et al.*, 2000). The overall SMR for colon cancer in this cohort was 1.83 (95%CI: 1.20–2.66). There was evidence for a positive dose–response relationship, in that excess mortality from colon cancer was confined to men who had worked as laggers or had been severely exposed for more than 2 years. This positive trend was statistically significant ($P = 0.017$).

In a cohort comprised of family members of men who had been employed in an asbestos-cement factory in Casale Monferrato, Italy, Ferrante *et al.* (2007) examined cancer mortality. Among women with domestic exposure to asbestos, 21 deaths from cancer of the "intestine and rectum" versus 16.0 expected (SMR, 1.31; 95%CI: 0.81–2.0) were observed. For cancer of the rectum, ten deaths versus five expected (SMR, 2.00; 95%CI: 0.96–3.69) were observed.

Several other cohort studies of occupationally exposed populations in a variety of industries have also found evidence for an association between asbestos exposure and cancer of the colorectum (Puntoni *et al.*, 1979: Hilt *et al.*, 1985; Jakobsson *et al.*, 1994; Raffn *et al.*, 1996; Szeszenia-Dabrowska *et al.*, 1998; Smailyte *et al.*, 2004).

Jakobsson *et al.* (1994) examined colon cancer by anatomical location in asbestos-cement workers, and observed an increased incidence of malignancy in the right side of the colon, but not in the left side.

A report on incidence of cancer of the colorectum from the Beta-Carotene and Retinol Efficacy Trial (CARET) found a relative risk of 1.36 (95%CI: 0.96–1.93) among 3987 heavy smoker participants occupationally exposed to asbestos as compared to smoker participants not exposed to asbestos (Aliyu *et al.*, 2005). Of note was the finding that the relative risk for cancer of the colorectum was 1.54 (95%CI: 0.99–2.40) among participants with asbestos-induced pleural plaques. The investigators interpreted the presence of pleural plaques as a marker for heavy individual exposure to asbestos. Risk for cancer of the colorectum also increased with worsening pulmonary asbestosis ($P = 0.03$ for trend). It was reported that a "dose–response trend based on years of asbestos exposure was less evident".

(b) *Case–control studies*

Evidence from case–control studies of asbestos and cancer of the colorectum is in general less strong than the evidence from the cohort studies. However, case–control studies from the Nordic countries and the USA have, however, reported significant increases in asbestos-associated odds ratios in occupationally exposed poulations (Fredriksson *et al.*, 1989; Gerhardsson de Verdier *et al.*, 1992; Vineis *et al.*, 1993; Kang *et al.*, 1997; Goldberg *et al.*, 2001).

Consideration of latency since first exposure appears to be an important factor in assessing these studies. Thus, Gerhardsson de Verdier *et al.* (1992) examined incidence of cancer of the colorectum by interval since first occupational exposure and observed "for subjects exposed to asbestos, the risks were highest when the latency period was more than 39 years." Gerhardsson de Verdier *et al.* observed further that the relative risk for cancer of the right colon was 2.6 (95%CI: 1.2–5.9) among workers exposed to asbestos, and that for malignancy of the left colon, only 0.5 (95%CI: 0.1–1.9).

Other cohort and case–control studies have not found evidence for an association between asbestos exposure and cancer of the colorectum (Gardner *et al.*, 1986; Hodgson & Jones, 1986; Garabrant *et al.*, 1992; Dement *et al.*, 1994; Demers *et al.*, 1994; Tulchinsky *et al.*, 1999; Hein *et al.*, 2007; Loomis *et al.*, 2009).

(c) *Meta-analyses*

Some of these meta-analyses have stratified studies according to the standardized mortality ratio for lung cancer or the percentage of deaths due to mesothelioma:

Morgan *et al.* (1985) found a summary standardized mortality ratio for cancer of the colorectum of 1.13 (95%CI: 0.97–1.30). This was reduced to 1.03 (95%CI: 0.88–1.21) after deleting cases in which the diagnosis of cancer of the colorectum was based on "best evidence" (pathological review) rather than death certificate data.

Frumkin & Berlin (1988) found in cohorts where the standardized mortality ratio for lung cancer was < 2.00 that the standardized mortality ratio for cancer of the colorectum was 0.86 (95%CI: 0.69–1.09). By contrast, when the standardized mortality ratio for lung cancer was > 2.00, the standardized mortality ratio for cancer of the colorectum increased to 1.61 (95%CI: 1.34–1.93).

Homa *et al.* (1994) found an elevated summary standardized mortality ratio for cancer of the colorectum in cohorts exposed to serpentine asbestos that had an standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.73; 95%CI: 0.83–3.63), and also in cohorts exposed to a mix of amphibole and serpentine asbestos that had a standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.48; 95%CI: 1.24–1.78). Among cohorts exposed to amphibole asbestos, the standardized mortality ratio for cancer of the colorectum was elevated regardless of the standardized mortality ratio for lung cancer. Homa *et al.* (1994) saw similar trends between standardized mortality ratio for cancer of the colorectum and percentage of deaths from mesothelioma.

Gamble (2008) reported that there was "tendency for CRC [cancer of the colorectum] risk ratios to be elevated when lung cancer risk ratios are >4" and further noted a significantly elevated standardized mortality ratio of 1.60 (95%CI: 1.29–2.00) for cancer of the colorectum when the standardized mortality ratio for lung cancer exceeds 3.00. Gamble (2008) observed no trend in cancer of the colorectum mortality with increasing percentage of deaths due to mesothelioma. Gamble saw no association between asbestos exposure and rectal cancer.

The IOM (2006) conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the colorectum. In studies that compared "any" versus no exposure, the summary relative risk was 1.15 (95%CI: 1.01–1.31). For studies comparing "high" versus no exposure, the lower-bound summary relative risk was 1.24 (95%CI: 0.91–1.69), and the upper-bound summary relative risk, 1.38 (95%CI: 1.14–1.67).

The IOM also conducted a meta-analysis of the published case–control studies. Overall, 13 studies comparing "any" versus no exposure yielded a summary relative risk of 1.16 (95%CI: 0.90–1.49).

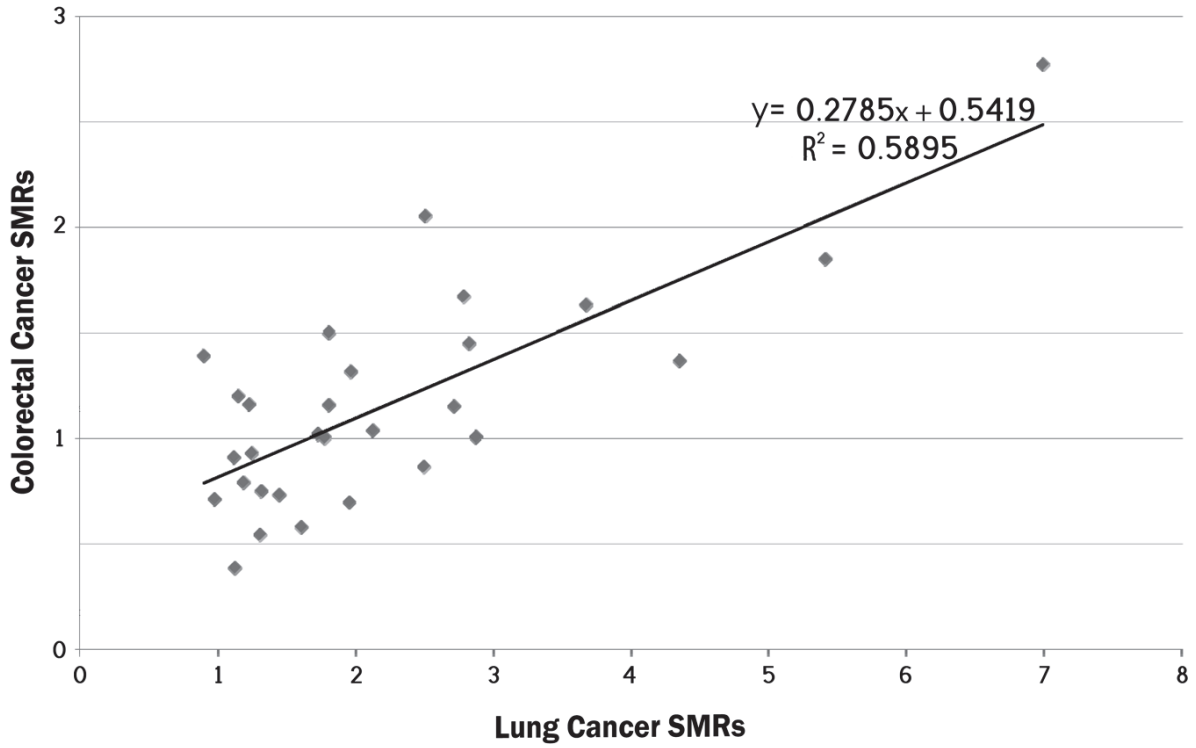
The *IARC Monograph* 100C Working Group developed a scatter plot comparing standardized mortality ratios for lung cancer with standardized mortality ratios for cancer of the colorectum in the same cohorts. The trend was positive with a correlation coefficient (r2) of 0.59, see Fig. 2.2.

(i) Asbestos in drinking-water and cancer of the colorectum

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the colon. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. No association between asbestos exposure and colon cancer was observed. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined colon cancer incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. The standardized incidence ratio for colon cancer in

Fig 2.2 Colorectal & lung cancer correlation in asbestos cohorts



Compiled by the Working Group

the entire cohort was 1.5 (95%CI: 0.9–2.2). In the subcohort with "definite" exposure to asbestos, the standardized incidence ratio was 0.8 (95%CI: 0.1–2.9). In those members of the definite exposure subcohort followed for 20+ years, the standardized incidence ratio was 1.6 (95%CI: 1.0–2.5).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and colon cancer and concluded that the data were inadequate to evaluate colon cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada and found no consistent pattern of association.

2.4.6 Cancer of the ovary

The published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse, because the workforce occupationally exposed to asbestos in such occupations as mining, milling shipyard work, construction and asbestos insulation work has been predominantly male. An examination of the association between asbestos and ovarian cancer was not undertaken by the IOM (2006).

See Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.8.pdf.

(a) Cohort studies

The Working Group examined 11 cohort studies that examined the association between asbestos exposure and ovarian cancer in 13 populations, ten with occupational exposure to asbestos and three with community-based or residential exposure.

Acheson *et al.* (1982) examined a cohort in the United Kingdom consisting of two groups of women in separate factories (n = 1327), employed in the manufacture of asbestos-containing gas masks before and during World War II. One factory had used crocidolite asbestos, and the other had used chrysotile. Among 757 women in the plant that used crocidolite, 12 deaths from ovarian cancer were observed versus. 4.4 expected (SMR, 2.75; 95%CI: 1.42–4.81). Among 570 women in the plant that used chrysotile asbestos, five deaths were observed for ovarian cancer versus 3.4 expected (SMR, 1.48; 95%CI: 0.48–3.44).

Wignall & Fox (1982) conducted a 30-year, follow-up mortality study of a population of 500 women in the United Kingdom employed in the manufacture of asbestos-containing gas masks before and during World War II. The type of asbestos used was crocidolite. A total of six deaths from ovarian cancer were obserevd versus. 2.8 expected (SMR, 2.13). When the cohort was subdivided according to degree of exposure to asbestos, the highest mortality from ovarian cancer was found among the subgroup definitely exposed to asbestos from the early 1940s (SMR, 14.81; $P < 0.01$). Overall five deaths from ovarian cancer were found among women definitely exposed to asbestos (versus 0.63 expected), whereas none were found among women definitely not exposed to asbestos (versus 0.40 expected).

To address potential misclassification of some deaths in this cohort recorded on death certificates as ovarian cancer as opposed to peritoneal mesothelioma, Wignall & Fox (1982) conducted a histopathological review of the cases cases of diagnosed ovarian cancer for which tissue material was available. One of these three cases was found to be peritoneal mesothelioma, while the diagnosis of ovarian cancer was sustained in the other two cases.

In a cohort study of 700 women factory workers employed in an asbestos-board insulation manufacturing company in the east end of London and followed for 30+ years, Berry *et al.* (2000) observed nine deaths from ovarian cancer versus 3.56 expected (SMR, 2.53; 95%CI: 1.16–4.80) (Berry *et al.*, 2000), with evidence for a positive exposure–response relationship. Among women with low-to-moderate exposure to asbestos, two deaths were observed versus 0.54 expected; in the subset with "severe" asbestos exposure of < 2 years' duration, two deaths were observed versus 2.12 expected. (SMR, 0.94); and among women with severe exposure of > 2 years' duration, five deaths from ovarian cancer were observed versus 0.90 expected (SMR, 5.35).

An assessment was performed of the significance of the positive exposure–response trend (P = 0.18). To address the potential misclassification of some deaths in this cohort having been recorded as ovarian cancer as opposed to peritoneal mesothelioma, Newhouse *et al.* (1972) conducted a histopathological review of the four deaths that by 1972 had been recorded as due to ovarian cancer; three of the four had occurred in women with severe and prolonged exposure to asbestos. Histological material was available for two of these cases. In both, the diagnosis of ovarian cancer was confirmed.

Reid *et al.* (2008) reported on cancer mortality in a cohort of 2552 women and girls who lived in the crocidolite asbestos mining town of Wittenoom in Western Australia during 1943–92, who were not involved in asbestos

mining and milling. Environmental contamination of the town with asbestos dust is reported to have been extensive. The women's exposure was environmental and not occupational. There were nine deaths from ovarian cancer in this cohort (SMR, 1.26; 95%CI: 0.58–2.40).

Reid *et al.* (2009) conducted a cancer incidence study in the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos. Additionally, they examined cancer incidence in 416 women who had worked in various capacities in the Wittenoom crocidolite asbestos mines and mills. Among community residents, ten incident cases of ovarian cancer were observed (SIR, 1.18; 95%CI: 0.45–1.91). Among women workers employed in the asbestos factory, one case of ovarian cancer was observed (SIR, 0.49; 95%CI: 0.01–2.74).

To address the possibility that some diagnosed cases of ovarian cancer in this cohort might in fact have been cases of peritoneal mesothelioma, Reid *et al.* (2009) examined pathological material from nine of their cases. The diagnosis of ovarian cancer was sustained in every case.

Pira *et al.* (2005) conducted a cohort study of 1077 women employed for at least one month during 1946–84 in an asbestos-textile factory in Italy, and followed up to 1996. A variety of types of asbestos were used in the factory, including crocidolite. A non-significantly increased standardized mortality ratio of 2.61 was observed for cancer of the ovary, based on five deaths. Among women in this cohort with ≥ 10 years of employment with asbestos, the standardized mortality ratio for ovarian cancer was 5.73, based on three deaths. Among women with ≥ 35 years since first employment, the standardized mortality ratio for ovarian cancer was 5.37, based on two deaths. This cohort was heavily exposed to asbestos, as supported by a standardized mortality ratio for lung cancer among women of 5.95, and by the occurrence of 19 deaths from mesothelioma (12%) among 168 total deaths in women.

Magnani *et al.* (2008) examined cancer mortality among a cohort of former workers at a now closed asbestos-cement factory in Casale Monferrato, Italy. A mix of crocidolite and chrysotile asbestos was used in this factory. Among women workers, there was an excess of ovarian cancers: nine observed versus 4.0 expected (SMR, 2.27; $P < 0.05$). Among women workers with 30 or more years exposure, the standardized mortality ratio for ovarian cancer was 2.97. Bertolotti *et al.* (2008) described the same findings in the same cohort [in Italian].

Ferrante *et al.* (2007) examined cancer mortality in a cohort consisting of family members of men who had been employed in the asbestos-cement factory in Casale Monferrato, Italy, described in the preceding paragraph. Exposure was to a mix of crocidolite and chrysotile. Among women with domestic exposure to asbestos, 11 deaths from ovarian cancer were observed versus 7.7 expected (SMR, 1.42; 95%CI: 0.71–2.54).

Germani *et al.* (1999) examined mortality from ovarian cancer in a cohort of 631 women workers in Italy who had been compensated for asbestosis. The type of fibre to which the women were exposed was not specified. In the total cohort, there were nine deaths from ovarian cancer (SMR, 4.77; 95%CI: 2.18–9.06). In the subset of women from the asbestos-textile industry, there were four deaths from ovarian cancer (SMR, 5.26; 95%CI: 1.43–13.47). In the subcohort from the asbestos cement industry, there were five deaths from ovarian cancer (SMR = 5.40; 95%CI: 1.75 – 12.61).

Rösler *et al.* (1994) examined cancer mortality in a cohort of 616 women workers in Germany who had been occupationally exposed to asbestos. Proportionate mortality was computed according to cause of death. A total of 95% of the asbestos used in Germany at this time was chrysotile, but the authors state that "admixture of crocidolite cannot be excluded, particularly in the manufacture of asbestos textile." Two deaths

from ovarian cancer were observed versus 1.8 expected (SMR, 1.09; 95%CI: 0.13–3.95).

(i) Population-based cohort studies

Vasama-Neuvonen *et al.* (1999) conducted a case–control study of ovarian cancer of occupational exposures in Finland. The asbestos fibre type was not specified and the standardized incidence ratio was 1.30 (95%CI: 0.9–1.80) between ovarian cancer and exposure to "high levels of asbestos."

Pukkala *et al.* (2009) examined the incidence of ovarian cancer among women employed in various occupational categories in Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Among the groups examined were plumbers, a group with known occupational exposure to asbestos. Fibre type was not specified. A total of four ovarian cancers were observed in these women plumbers. The standardized incidence ratio was 3.33 (95%CI: 0.91–8.52)

(b) Case–control studies

Langseth & Kjærheim (2004) conducted a nested case–control study to examine the association between asbestos exposure and ovarian cancer within a cohort of female pulp and paper workers in Norway that had previously been found to have excess mortality from ovarian cancer (37 ovarian cancers observed versus 24 expected; SIR, 1.50; 95%CI: 1.07–2.09). The asbestos fibre type was not specified. In the case–control study, the odds ratio for occupational exposure to asbestos, based on 46 cases of ovarian cancer, was 2.02 (95%CI: 0.72–5.66).

2.5 Synthesis

The Working Group noted that a causal association between exposure to asbestos and cancer of the larynx was clearly established, based on the fairly consistent findings of both the occupational cohort studies as well as the case-controlcase–control studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and laryngeal cancer-cancer of the larynx reported in several of the well-conducted cohort studies. This conclusion was further supported by the meta-analyses of 29 cohort studies encompassing 35 populations and of 15 case-controlcase–control studies of asbestos exposure and laryngeal cancercancer of the larynx undertaken by the IOM (2006). However, there is insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause laryngeal cancercancer of the larynx.

The Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos (Acheson *et al.*, 1982; Wignall & Fox, 1982; Germani *et al.*, 1999; Berry *et al.*, 2000; Magnani *et al.*, 2008). The conclusion received additional support from studies showing that women and girls with environmental, but not occupational exposure to asbestos (Ferrante *et al.*, 2007; Reid *et al.*, 2008, 2009) had positive, though non-significant, increases in both ovarian cancer incidence and mortality.

The Working Group carefully considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer, and that these contributed to observed excesses. Contravening that possibility is the finding that three of the studies cited here specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases. The Working Group noted that the possibility of diagnostic misclassification had probably diminished in recent years because of the development of new immunohistochemical diagnostic techniques.

The conclusion of the Working Group received modest support from the findings of

non-significant associations between asbestos exposure and ovarian cancer in two case–control studies (Vasama-Neuvonen *et al.*, 1999; Langseth & Kjærheim, 2004).

And lastly, the finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with household exposure to asbestos (Heller *et al.*, 1996) or with occupational exposure to asbestos (Langseth *et al.*, 2007).

The study by Heller *et al.* (1996) was a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure. The study found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight). By contrast, only one of the 17 women without household exposure had counts in that range.

The study by Langseth *et al.* (2007) found approximately 3–4 × 105 asbestos fibres per gram (net weight) in normal ovarian tissue taken from 2/46 patients with ovarian adenocarcinoma. It is unclear how many of these fibres were verified as asbestos because it is stated in the publication that three chrysotile and one crocidolite asbestos fibres were identified in Case 1, and two anthophyllite and one chrysotile fibre were identified in Case 2. This small number of confirmed asbestos fibres in only two of the patients could be due to sample contamination. Technical caveats associated with quantification of asbestos fibre tissue burdens are discussed in Section 4 of this *Monograph* and in IOM (2006).

Further discussion of the biological plausibility of an association between asbestos exposure and ovarian cancer is to be found in Section 4 of this *Monograph*.

The Working Group noted a positive association between exposure to abestos and cancer of the pharynx, based on the fairly consistent positive findings in a series of well conducted cohort studies of populations occupationally exposed to asbestos (Selikoff & Seidman, 1991; Sluis-Cremer *et al.*, 1992; Reid *et al.*, 2004; Pira *et al.*, 2005) as well as on the positive findings of three case–control studies (Zheng *et al.*, 1992; Marchand *et al.*, 2000; Berrino *et al.*, 2003). This conclusion was further supported by the findings of the meta-analysis conducted by the IOM. While tobacco smoking and alcohol consumption are clearly the dominant risk factors for cancer of the pharynx in industrialized countries, these associations between cancer of the pharynx and asbestos remained evident in several studies when tobacco and alcohol exposures were considered. The Working Group observed that the strongest associations between asbestos exposure and cancer of the pharynx were seen in studies that specifically examined cancer of the hypopharynx, the portion of the pharynx that is located closest to the larynx. However, there is insufficient information in the published literature to discern whether there are any differences among asbestos fibre types in their ability to cause cancer of the pharynx.

The Working Group noted a positive association between exposure to abestos and cancer of the stomach, based on the positive associations between asbestos exposure and death from stomach cancer observed in several of the cohort studies with heaviest asbestos exposure (Selikoff *et al.*, 1964; Enterline *et al.*, 1987; Raffn *et al.*, 1989; Liddell *et al.*, 1997; Musk *et al.*, 2008). The conclusion was further supported by the positive dose–response relationships observed between cumulative asbestos exposure and stomach cancer mortality in several cohort studies (Selikoff & Hammond., 1979; Zhang & Wang, 1984; Liddell *et al.*, 1997; Pang *et al.*, 1997). It was supported by the results of two large and well performed meta-analyses (Frumkin & Berlin, 1988; Gamble, 2008). It received borderline support from the IOM meta-analysis of cohort

studies, and also from the IOM meta-analysis of case–control studies, which show an especially strong relationship when only extreme exposures are considered. It was supported by the comparison developed by the Working Group between standardized incidence ratios for lung cancer and stomach cancer.

Positive associations between asbestos exposure and stomach cancer and positive dose–response relationships are most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and stomach cancer, even if such an association were truly present.

[The Working Group noted that heavy occupational exposure to dust, as had likely occurred in the case of the Quebec asbestos cohort, could have been an effect modifier. Low socioeconomic status is also a potential confounder.]

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause stomach cancer. In the study by Liddell *et al.* (1997) exposure was to virtually pure chrysotile asbestos, in the study by Musk *et al.* (2008) the exposure was predominantly to crocidolite, and in most of the other published studies that observed positive associations, populations were exposed to mixtures of different asbestos fibres.

The Working Group noted a positive association between exposure to abestos and cancer of the colorectum, based on the fairly consistent findings of the occupational cohort studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and cancer of the colorectum consistently reported in the more detailed cohort studies (McDonald *et al.*, 1980; Albin *et al.*, 1990; Berry *et al.*, 2000; Aliyu *et al.*, 2005). The conclusion was further supported by the results of four large and well performed meta-analyses (Frumkin & Berlin 1988; Homa *et al.*, 1994; IOM, 2006; Gamble, 2008).

Positive exposure–response relationships between asbestos exposure and cancer of the colorectum appear most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and cancer of the colorectum, even if such an association were truly present.

The apparently non-positive findings of several the case–control studies are not a deterrent to this conclusion. The majority of these case–control studies incorporated relatively little information on levels of asbestos exposure; indeed, most of them considered exposure as simply a dichotomous yes/no variable. Some of the case–control studies also may be compromised by inadequate duration of follow-up. Thus, the Garabrant study (Garabrant *et al.*, 1992) may be subject to the criticism, offered by Gerhardsson de Verdier *et al.* (1992) that "the highest duration of exposure…was 'at least 15 years,' a period that may be too short to detect an elevated risk."

There is some suggestion in the literature that the association between asbestos might be stronger for colon cancer than for rectal cancer. This view is supported by the meta-analysis of Gamble (2008) which found a positive dose–response relationship for cancer of the colorectum taken together, but not for rectal cancer. It is supported also by the study of Jakobsson *et al.* (1994), which found excess of cancer of the right colon in asbestos-exposed workers, but not of the left colon.

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause cancer of the colorectum. It is of note in the study by McDonald *et al.* (1980) that exposure was to virtually pure chrysotile asbestos, whereas in most of the other studies cited above, populations were exposed to mixtures of different asbestos fibres.

3. Cancer in Experimental Animals

3.1 Introduction

Asbestos is a collective name for six different types of fibres: chrysotile, crocidolite, amosite, anthophyllite, tremolite, actinolite (see Section 1). Dusts from various deposits of the same type of asbestos can cause variations in the severity of the effects observed. Erionite is a fibrous zeolite found in Central Anatolia (Turkey), and Oregon (USA) (see Section 1 of the *Monograph* on Erionite). Talc is a hydrated magnesium silicate, and talc ore may contain several other minerals including anthophyllite, tremolite, calcite, dolomite, magnesite, antigorite, quartz, pyrophyllite micas, or chlorites (see Section 1).

The definition of pathogenic fibre properties as "sufficiently long, thin, and durable" is the subject of much debate, as are the differences between the exposure–response relationships or retained dose–response relationships of asbestos fibres in man and in rats, and the potential differences in the carcinogenicity of chrysotile compared to the various amphibole asbestos types. One of the reasons for a potential difference is a difference in the biopersistence between the two asbestos groups mentioned. The biopersistence is higher in the amphibole group (Hesterberg *et al.*, 1996, 1998a, b). The rat is the main test model for fibre-induced diseases. As the removal of asbestos fibres due to biosolubility is slow compared to the lifetime of rats and hamsters, experiments with this model may not be appropriate in predicting results of risk in humans (Berry, 1999).

Critical fibre dimensions to be used in toxicology and occupational regulations were discussed by the Working Group. It is generally agreed that the carcinogenic potency of a fibre increases with fibre length. Apart from the ongoing scientific view, standards of regulated fibres, with few exceptions, are based on the WHO fibre definition: aspect ratio ≥ 3: 1, length ≥ 5 µm, diameter ≤ 3 µm.

The tested materials (asbestos and erionite) are not presented in separate tables as in many cases they were tested in parallel experiments. The reason to split the inhalation studies into two tables (Table 3.1; Table 3.2) is that in many studies, various asbestos fibres were used as positive control in studies in which man-made fibres were tested (Table 3.2). In these latter studies, normally only one asbestos concentration was used. As for intrapleural and intraperitoneal studies, Table 3.4 is separate from Table 3.5 because the studies of Stanton *et al.* (1981) (see Table 3.5) included many fibre types – which also included fibres not to be reviewed here – and was designed to investigate the effect of fibre length and fibre type on mesothelioma induction.

A general evaluation on the type of fibre application in animal studies and an evaluation of some of the asbestos studies listed in Tables 3.1–3.5 can be found in Pott (1993) and IARC (2002).

3.2 Inhalation exposure

Table 3.1 and Table 3.2 give an overview of the numerous inhalation experiments on asbestos, and a few experiments on erionite. Some of these are described more extensively below.

Bronchial carcinomas and pleural mesotheliomas have been observed in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in

tumour incidence at other sites. [The Working Group noted that in many studies, no complete histopathology was done.] All relatively short UICC asbestos preparations showed chronic effects in lung (based on fibre lenghts > 5 μm in the dust chamber) for fibres quantitatively roughly the same.

One of the first inhalation study with asbestos in rats that showed exposure–response relationships is the experiment of Wagner *et al.* (1974). Wistar rats were exposed to 10–15 mg/m^3 of one of the five UICC standard asbestos samples for 7 hours per day, mostly 5 days per week. The duration of exposure lasted from one day to 24 months. According to the reported data, in the group exposed to crocidolite for one day, lung tumours and one mesothelioma were found in 7/43 rats (16%). The corresponding exposure to chrysotile A (from Canada) resulted in lung tumours in 5/45 rats; for amosite 4/45 rats developed lung tumours and one mesothelioma. Three months of exposure to the five UICC standard asbestos samples resulted in the following thoracic tumour (mainly of the lung) incidences: chrysotile A, 44%;chrysotile B (from Zimbabwe), 53%; crocidolite, 42%; amosite, 27%; anthophyllite, 16%. Further results are listed in Table 3.1. In the 126 control rats, seven animals were also found to have lung tumours (Table 3.3). This high spontaneous lung tumour rate is a unique finding in Wistar rats. A review of unexposed control groups of many other studies shows that spontaneous lung tumours are very rare in this rat strain (Pott *et al.*, 1995; Table 3.3); on average, the incidence is less than one percent. Therefore, the very high tumour incidences described in this first inhalation study of Wagner *et al.* (1974) might be a misinterpretation of histopathological lesions because of a lack of experience at that time.

In a study conducted by Davis *et al.* (1978), five groups of Wistar rats were exposed to chrysotile (2.0, 10 mg/m^3), crocidolite (5.0, 10 mg/m^3), or amosite (10 mg/m^3). The highest tumour incidences (21–38%) were found in the chrysotile-exposed animals. This may be due to the relatively high fraction of fibres longer than 20 μm in the chrysotile dust used in this experiment. In addition to the lung tumours, extrapulmonary neoplasms included a relatively large number of peritoneal connective tissue tumours.

In a further study by Davis *et al.* (1986b), inhalation of short-fibred amosite did not produce tumours in Wistar rats (0/42). In contrast, there was a tumour incidence of 13/40 (33%) in a group exposed to long-fibred amosite. [The Working Group noted that extensive milling to produce short fibres may have altered the surface reactivity, see Section 4].

A group of 48 SPF Fischer rats was exposed to 10 mg/m^3 UICC chrysotile B by inhalation for 7 hours per day, 5 days per week, for 12 months (Wagner *et al.*, 1984b). This group served as positive controls in a study in which various man-made fibres were tested. After exposure, the animals were kept until natural death. Twelve thoracic tumours (one adenoma, 11 adenocarcinomas) were observed in 48 rats. In the untreated control group, no lung tumours were observed in 48 rats.

Smith *et al.* (1987) exposed groups of 58 female Osborne-Mendel rats to 7 mg/m^3 UICC crocidolite asbestos for 6 hours per day, for 5 days per week, for 2 years. After this treatment, rats were observed for life. The tumour incidence in rats exposed to crocidolite was 3/57 (one mesothelioma and two carcinomas). In the control group, no tumours were observed in 184 rats.

Special attention should be drawn to the crocidolite study with male Fischer rats of McConnell *et al.* (1994) because this study is very well documented. The exposure to 10 mg dust/m^3 (with 1610 WHO fibres/mL containing 236 fibres > 20 μm) for 6 h per day, 5 days per week had to be stopped after 10 months because of unexpected mortality, which was interpreted as a sign that the maximum tolerated dose had been exceeded. The number of WHO fibres per μg dry

Table 3.1 Studies of cancer in experimental animals exposed to various asbestos species and erionite (inhalation exposure)[a]

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Asbestos									
Chrysotile, Canada	86	NR	White rats 16 months or longer	6 h/d 5 d/wk 62 wk	0	10/41[c]	24		Gross *et al.* (1967)
Crocidolite	50	1105	Sprague-Dawley rats lifetime	4 h/d 4 d/w 24 mo	0	5/46	11		Reeves *et al.* (1974)
Chrysotile UICC/A	14.7	NR	Wistar rats lifetime	7 h/d 1 d	0	5/45	11		Wagner *et al.* (1974)
	12.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	16/36	44		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	8/19	42		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	19/27	70		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	11/17	65		

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/B	9.7	NR	Wistar rats lifetime	7 h/d 1 d	0	1/42	2		
	12.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	18/34	53		
	10.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	5/17	29		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	3	14/23	61		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	11/21	52		
Crocidolite UICC	12.5	NR	Wistar rats lifetime	7 h/d 1 d	1	7/43	16		
	12.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	1	15/36	42		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	4/18	22		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/26	77		
	10.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/18	72		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Amosite UICC	14.1	NR	Wistar rats lifetime	7 h/d 1 d	1	4/45	9		
	12.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	10/37	27		
	11.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	2/18	11		
	10.8	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	10/25	40		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/21	62		
Anthophyllite UICC	12.8	NR	Wistar rats lifetime	7 h/d 1 d	0	2/44	5		
	13.5	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	6/37	16		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	6/18	33		
	11.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	21/28	75		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	17/18	94		
Amosite UICC	10	550	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/43	5		Davis *et al.* (1978)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Crocidolite UICC	5	430	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	3/43	7		
	10	860	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	1/40	3		
Chrysotile SFA	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	1	1/40	3		Wagner *et al.* (1980)
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	4/18	22		
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	8/22	36		
Chrysotile grade 7	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	1/39	3		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	5/18	28		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	3/24	13		
Chrysotile UICC (/B)	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	4/40	10		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	10/18	56		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	6/23	26		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC /A	2	390	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	9/42	21		Davis *et al.* (1978)
Chrysotile UICC /A	10	1950	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/40	38		
Chrysotile UICC	9	NR	Wistar rats lifetime	7 h/d 1 d/wk 12 mo	0	6/43	14	Peak dosing (one d/wk); no control group	Davis *et al.* (1980a)
Amosite UICC	50	NR	Wistar rats lifetime	7 h/d 1 d/w 12 mo	0	6/44	14	Peak dosing (one d/wk); no control group	
Chrysotile UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/43 (8 malignant, 7 benign)	35	No control group	Davis *et al.* (1980b)
Chrysotile "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	11/42 (3 maligant, 8 benign)	26	No control group	
Amosite "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/37	0	No control group	
Amosite UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/40	5	No control group	
Tremolite	10	1600	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/39	51		Davis *et al.* (1985)
Crocidolite UICC	10	1630/350[d]	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	1/28	4		Wagner *et al.* (1985)
Chrysotile WDC textile yarn	3.5	679	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	18/41	44		Davis *et al.* (1986a)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile factory WDC	3.7	468	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	21/44	48		
Chrysotile textile yarn	3.5	428	Wistar rats lifetime	7 h/d 5 /wk 12 mo	1	16/42	38		
Chrysotile experimental WDC	3.5	108	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	4	21/43	49		
Chrysotile experimental WDC reversed daylight	3.8	111	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	18/37	49		
Amosite "long"	10	2060/1110[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	13/40	33		Davis *et al.* (1986b)
Amosite "short"	10	70/12[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/42	0		
Crocidolite UICC	10	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	1/28	4		Wagner *et al.* (1987)
Chrysotile, Canada, "long"	10	5510/1930[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	22/40	55	1 peritoneal mesothelioma was observed in addition	Davis & Jones (1988)
Chrysotile, Canada, "short"	10	1170/330[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	7/40	18	1 peritoneal mesothelioma was observed in addition	
Chrysotile UICC/A "discharged"	10	2670	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	11/39	28		Davis *et al.* (1988)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	14/36	39		
Chrysotile UICC /A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	13/37	35		Davis *et al.* (1991a)
Chrysotile UICC /A	10	2545	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	26/41	63	Increase of tumour rate by particulate dust	
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile UICC /A	10	1960	Wistar rats lifetime	5 h/d 5 d/w 12 mo	6	22/38	58	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	3648	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	20/40	50	Increase of tumour rate by particulate dust	Davis *et al.* (1991a)
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	4150	Wistar rats lifetime	5 h/d 5 d/w 12 mo	8	26/39	67	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile Jeffrey	11	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	20/52	38		Mc Connell *et al.* (1991)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile	NR	NR	Baboons 6 yr	6 h/d 5 d/wk 4 years	0	0/6[e]	0		Goldstein & Coetzee (1990)
Crocidolite UICC	12-14	1130-1400	Baboons 6 yr	6 h/d 5 d/wk 4 yr	3	3/21[f]	14		
Amosite UICC	7	1110	Baboons 6 yr	6 h/d 5 d/wk 4 yr	2	2/11[f]	18		Goldstein & Coetzee (1990), Webster *et al.* (1993)
Erionite									
Erionite, Oregon	10	354	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	27	27/28	96		Wagner *et al.* (1985)
Erionite, Oregon	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	24	24/27	89	No control group	Wagner (1990)
Erionite, Oregon "short"	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	0/24	0	No control group	

[a] negative control groups: see Table 3.3

[b] Animals with benign or malignant lung tumour or pleural mesothelioma. The percentage of animals with tumours is related to the number of rats examined which were alive at a certain point in time (e.g. at the beginning of the experiment or after one year, or at the point in time of the death of the first animal with a tumour). Often, this is not clearly specified.

[c] observation time ≥6 mo

[d] Fibre count refers to fibres with lengths > 10 µm and diameters < 1 µm, in the aerosol

[e] observation time ≥4 yr

[f] observation time ≥5 yr

d, day or days; h, hour or hours; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

From Pott & Roller (1993b)

Table 3.2 Studies of cancer in experimental animals in which asbestos was used as positive control group (in inhalation studies of various man-made mineral fibres)

Test substance	Concentration (mg/m^3)	Aerosol fibres per cm^3 (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Amosite	NR	981 89 f > 20 µm/cm^3	AF/HAN rats, 24 mo	7 h/d 5 d/wk 12 mo	2	18/42 (7 carcinomas, 9 adenomas)	43		Davis *et al.* (1996), Cullen *et al.* (2000)
Chrysotile UICC/B	10	NR	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	11/56 (7 adenocarcinomas, 4 adenomas)	20		McConnell *et al.* (1984)
Chrysotile UICC/B	10	3832/1513[b]	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	12/48 (11 adenocarcinomas, 1 adenoma)	25		Wagner *et al.* (1984b)
Chrysotile NIEHS, Canada	10	10 600	Fischer rats, 24 mo	6 h/d 5 d/wk 24 mo	1	14/69	20		Hesterberg *et al.* (1993)
Crocidolite	10	1610	Fischer 344/N rats, 24 mo	6 h/d 5 d/wk 10 mo	1	14/106 (10 adenomas, 5 carcinomas)	13		McConnell *et al.* (1994)
Crocidolite UICC	7	3000/90[b]	Osborne-Mendel rats, lifetime	6 h/d 5 d/wk 24 mo	1	3/57 (1 mesothelioma, 2 carcinomas)	5		Smith *et al.* (1987)
Chrysotile UICC/A	Cumulative dose: 13 800 mg.h/m^3	NR	Rats, lifetime	6 h/d 5 d/wk 18 mo	0	9/39 (5 adenomas, 1 adenocarcinoma, 3 squamous cell carcinomas)	23	Strain not specified	Pigott & Ishmael (1982)
Amosite UICC	300	3090	Sprague-Dawley rats, 18–24 mo	6 h/d 5 d/wk 3 mo	0	3/16[c]	19	Small number of animals; D= 0.4 µm	Lee *et al.* (1981), Lee & Reinhardt (1984)
Chrysotile, Canada	5	5901	Wistar rats, 24 mo	5 h/d 5 d/wk 12–24 mo	0	9/47	19		Le Bouffant *et al.* (1987)
Chrysotile Calidria	6	131	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	0/50	0		Muhle *et al.* (1987)

Table 3.2 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per cm³ (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Crocidolite, South Africa	2.2	162	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	1/50	2		Muhle *et al.* (1987)
Amosite UICC	300	3090	Syrian golden hamsters, 18–24 mo	6 h/d 5 d/wk 3 mo	0	0/12	0	Small number of animals diameter, 0.4 µm	Lee *et al.* (1981), Lee & Reinhardt (1984)
Crocidolite UICC	7	3000/90[b]	Syrian golden hamsters, lifetime	6 h/d 5 d/wk 24 mo	0	0/58	0		Smith *et al.* (1987)
Amosite	0.8	36 WHO f/cm³ 10 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	3	3/83	3.6		McConnell *et al.* (1999)
	3.7	165 WHO f/cm³ 38 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	22	22/85	26		
	7.1	263 WHO f/cm³ 69 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	17	17/87	20		
Crocidolite UICC	13.5	1128	Baboons lifetime	7 h/d 5 d/wk 40 mo	0	0/10	0	All males	Goldstein *et al.* (1983)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma
[b] Number of fibres with a length > 10 µm and a diameter < 1 µm in the aerosol
d, day or days; f, fibre; h, hour or hours; mo, month or months; NR, not reported; RCF, refractory ceramic fibre; wk, week or weeks
From Pott & Roller (1993b)

Table 3.3 Negative controls (clean air for lifetime) in carcinogenicity studies after inhalation exposures from Table 3.1 and Table 3.2

Species and strain	Number of pleural mesothelioma	No. of animals with thoracic tumours[a]/ No. of animals	Reference
Fischer rats	0	0/48	Wagner *et al* (1984b)
Fischer rats	0	0/28	Wagner *et al.* (1985)
Fischer rats	0	0/28	Wagner *et al.* (1987)
Fischer rats	0	1/56	McConnell *et al.* (1991)
Fischer rats	0	4/123	Hesterberg *et al.* (1993)
Fischer rats	0	2/126	McConnell *et al.* (1994)
Osborne-Mendel rats	0	0/184	Smith *et al.* (1987)
Sprague-Dawley rats	0	1/5	Reeves *et al.* (1974)
Sprague-Dawley rats	0	0/19	Lee *et al.* (1981)
White rats	0	0/25	Gross *et al.* (1967)
Wistar rats	0	7/126	Wagner *et al.* (1974)
Wistar rats	0	0/20	Davis *et al.* (1978)
Wistar rats	0	1/71	Wagner *et al.* (1980)
Wistar rats	0	0/36	Davis *et al.* (1985)
Wistar rats	0	2/39	Davis *et al.* (1986a)
Wistar rats	0	0/25	Davis *et al.* (1986a)
Wistar rats	0	0/110	Muhle *et al.* (1987)
Wistar rats	0	2/36	Davis *et al.* (1988)
Wistar rats	0	0/25	Davis *et al.* (1988)
Wistar rats	0	2/47	Davis & Jones (1988)
Wistar rats	0	2/47	Davis *et al.* (1991a)
Syrian golden hamsters	0	1/170	Smith *et al.* (1987)
Syrian golden hamsters	0	0/83	Mc Connell *et al.* (1999)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma

lung tissue was 1850 (73 fibres > 20 µm) at the end of exposure and 759 WHO fibres (41 fibres > 20 µm) 12 months later. Fourteen out of 106 rats (13.2%), which survived the second year or longer, died with lung tumour (five of these rats developed lung carcinomas), and one rat also developed a mesothelioma. In the control group, 2/126 rats developed lung adenomas.

In two lifetime studies, male and female Fischer rats were exposed to either 10 mg/m^3 erionite (Wagner *et al.*, 1985) or an unknown concentration of erionite (Wagner, 1990) for 6 hours per day, 5 days per week, for 12 months. Twenty seven out of 28 rats, and 24/27 rats developed pleural mesotheliomas, respectively. No lung tumours were observed. [The Working Group noted the lack of control group in the study by Wagner (1990).]

McConnell *et al.* (1999) exposed three groups of 125 male Syrian golden hamsters to 0.8, 3.7 and 7.1 mg/m^3 amosite for 6 hours per day, 5 days per week, for 78 weeks. They were then held unexposed for 6 weeks. Among animals that survived for at least 32 weeks, 3/83, 22/85 and 17/87 developed pleural mesotheliomas, respectively. No mesotheliomas were observed in 83 untreated controls and no lung tumours were observed in any groups.

Some experiments were reported with baboons. After amosite exposure and crocidolite exposure for 4 years, 2/11 baboons and 3/21 baboons developed pleural mesothelioma,

respectively (Goldstein & Coetzee, 1990; Webster *et al.*, 1993).

3.3 Intrapleural and intraperitoneal administration

Animal experiments had shown that an intrapleural injection of a suspension of asbestos dusts in rats leads to mesotheliomas (Wagner, 1962; Wagner & Berry, 1969). The serosa has subsequently been taken as a model for the examination of the carcinogenicity of fibrous dusts in numerous studies. Some groups have opted for administration into the pleural cavity, others preferring intraperitoneal injection of dust suspensions. In comparison with the intrapleural model, the intraperitoneal carcinogenicity test on fibres has proven to be the method with the far greater capacity and, consequently, the greater sensitivity (see also Pott & Roller, 1993a). Results from these numerous experiments using asbestos and erionite are listed in Table 3.4.

Table 3.5 contains a summary of the experiments by Stanton *et al.* (1981). In this extensive study, the authors implanted 72 dusts containing fibres of various sizes in the pleura of Osborne-Mendel rats. The probability of the development of pleural mesotheliomas was highest for fibres with a diameter of less than 0.25 µm and lengths greater than 8 µm.

In summary, samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelima induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

3.4 Intratracheal administration

Only a few studies have been carried out with intratracheal instillation of asbestos fibres in rats (Pott *et al.*, 1987; Smith *et al.*, 1987), and hamsters (Pott *et al.*, 1984; Feron *et al.*, 1985; Smith *et al.*, 1987). Principally, in this experimental model, asbestos fibres induced lung tumours in rats, and lung tumours and mesotheliomas in hamsters. Studies in hamsters are described below.

In a 2-year study, a group of male Syrian golden hamsters [initial number unspecified] was intratracheally instilled with 1 mg UICC crocidolite in 0.15 mL saline once a week for 8 weeks. At the end of the experiment, the incidences of lung carcinomas and of pleural mesotheliomas were 9/142 [$P < 0.01$] and 8/142 [$P < 0.01$], respectively. No thoracic tumours were observed in 135 titanium-dioxide-treated control animals (Pott *et al.*, 1984).

In a lifetime study, a group of Syrian golden hamsters [sex and initial number unspecified] was intratracheally instilled with 2 mg UICC crocidolite in 0.2 mL saline once a week for 5 weeks. At the end of the experiment, 20/27 animals developed broncho-alveolar tumours ($p<0.05$), including 7/27 with malignant tumours [$p<0.05$]. No broncho-alveolar tumours were observed in 24 saline-treated controls (Smith *et al.*, 1987).

3.5 Oral administration

A study on the carcinogenicity of ingested asbestos fibres involved male F344 rats groups exposed to amosite or chrysotile in combination with subcutaneous administration of a known intestinal carcinogen, azoxymethane (10 weekly injections of 7.4 mg/kg body weight). Fibres were administered three times a week for 10 weeks by intragastric bolus dosing (10 mg in 1 mL saline). The first experiment in this study included a full set of appropriate control groups. The experiment was terminated at 34 weeks. Neither amosite nor UICC chrysotile B, in combination with azoxymethane, increased the incidence of any intestinal tumours (≈10%) above that produced by azoxymethane alone, but the combination with either fibre type produced 4–5-fold increases

(not significant, $P > 0.1$) in metastatic intestinal tumours. A second experiment with larger groups, the same dosing regimen, and for lifetime, but with a more limited design, tested only amosite in combination with azoxymethane versus azoxymethane. Amosite did not enhance azoxymethane-induced intestinal tumours (incidence, 77% versus 67%) (Ward *et al.*, 1980; IOM, 2006). [The Working Group noted that the lack of untreated vehicle controls in the second experiment made interpretation of the results difficult considering that, compared to historical controls, there was a non-significant increase in intestinal tumours in rats exposed only to amosite (≈33%). One cannot know whether the results observed were associated with the asbestos or with irritation from the procedure, although one would not anticipate that gavage itself would impact the lower portion of the gastrointestinal tract.]

The most definitive animal studies of oral exposure to asbestos were a series of lifetime studies conducted by the National Toxicology Program (NTP, 1983, 1985, 1988, 1990a, b), in which asbestos (chrysotile, crocidolite, and amosite) was administered in the feed of rats and hamsters. Nonfibrous tremolite was also tested in rats according to the same protocol (NTP, 1990c). Exposure of dams of the study animals (1% in the diet) was followed by exposure of the pups by gavage (0.47 mg/g water) while they were nursing, and then in the diet for the remainder of their lives: they were exposed to asbestos at the level of 1%, which was estimated by the investigators to be about 70000 times the greatest possible human exposure in drinking-water. Histopathological examination of the entire colorectum was performed. No increases in the incidence of gastrointestinal lesions (inflammatory, preneoplastic, or neoplastic) were found after exposure to intermediate-length chrysotile (from Quebec) in hamsters, to short chrysotile (from New Idria) in rats or hamsters, to amosite in rats or hamsters, to crocidolite in rats, or to non-fibrous tremolite in rats. The mesentery was examined in detail, as well as mesenteric lymph nodes and sections of the larynx, trachea, and lungs from every animal. No lesions were found in any of those tissues. The only finding of note in the gastrointestinal tract was a slight increase in the incidence of adenomatous polyps in the large intestine after exposure to the intermediate-length chrysotile (from Quebec) in male rats (9/250 versus 0/85, $P = 0.08$), but preneoplastic changes in the epithelium were not found (NTP, 1985; IOM, 2006).

3.6 Intragastric administration

White rats, 2–3 months old, were surgically applied, on the greater curvature of the stomach, a perforated capsule containing 0 (control) or 100 mg chrysotile asbestos in a filler (beef fat: natural wax, 1:1). Tumours observed in 18/75 asbestos-exposed rats, between 18–30 months after the beginning of the experiment, were the following: eight gastric adenomas, two gastric adenocarcinomas, one gastric carcinoma, one cancer of the forestomach, one small intestine adenocarcinoma, two peritoneal mesotheliomas, and three abdominal lymphoreticular sarcomas. No tumours were observed in 75 control animals (Kogan *et al.*, 1987). [The Working Group noted various unresolved questions regarding the design of this study in particular the very high dose of 100 mg.]

3.7 Studies in companion animals

Mesotheliomas were reported in pet dogs with asbestos exposure in the households of their owners. Eighteen dogs diagnosed with mesothelioma and 32 age-, breed- and gender-matched control dogs were investigated. Sixteen owners of cases and all owners of controls were interviewed. An asbestos-related occupation or hobby of a household member was significantly associated with mesothelioma observed in cases (OR,

Table 3.4 Studies of cancer in rats exposed to asbestos fibres and erionite (intrapleural and intraperitoneal administration)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Asbestos	**Asbestos type**							
Wistar – Pott *et al.* (1989)	Actinolite	0.25	i.p.	0.1	20/36	56	***	
Wistar – Wagner *et al.* (1973)	Amosite UICC	20	i.pl.	NR	11/32	34	***	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.01	i.p.	0.0003	4/48	8	*	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.05	i.p.	0.002	8/32	25	***	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.5	i.p.	0.02	15/32	47	***	
Wistar – Wagner *et al.* (1973)	Anthophyllite UICC	20	i.pl.	NR	8/32	25	***	
Wistar – Wagner *et al.* (1973)	Chrysotile UICC/A	20	i.pl.	NR	7/31	23	***	
Sprague-Dawley – Monchaux *et al.* (1981)	Chrysotile UICC/A	20	i.pl.	NR	14/33	42	***	
Sprague-Dawley – Wagner *et al.* (1984b)	Chrysotile UICC/A	20	i.pl.	19.6	6/48	13	**	
Wistar – Pigott & Ishmael (1992)	Chrysotile UICC/A	20	i.pl.	NR	7/48	15	***	
Fischer – Coffin *et al.* (1992)	Chrysotile UICC/A	0.5	i.pl.	0.90	118/142 [d]	78	***d	
		2		3.6		87		
		4		7.2		92		
		8		14		83		
		16		29		83		
		32		57		75		
Wistar – Wagner *et al.* (1973)	Chrysotile UICC/B	20	i.pl.	NR	10/32	31	***	
Wistar – Wagner *et al.* (1980)	Chrysotile UICC/B	20	i.pl.	NR	5/48	10	*	
Fischer – Wagner *et al.* (1987)	Chrysotile UICC/B	20	i.pl.	NR	19/39	49	***	
Wistar – Pott *et al.* (1989)	Chrysotile UICC/B	0.25	i.p.	0.2	23/34	68	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.01	i.p.	0.002	2/48	4	NS	
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.05	i.p.	0.009	12/32	38	***	
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.5	i.p.	0.09	26/32	81	***	
Wistar – Wagner *et al.* (1973)	Crocidolite UICC	20	i.pl.	NR	19/32	59	***	
Fischer – Wagner *et al.* (1987)	Crocidolite UICC	20	i.pl.	NR	34/40	85	***	
Fischer – Wagner (1990)	Crocidolite UICC	20	i.pl.	NR	24/32	75	***	
Sprague-Dawley – Monchaux *et al.* (1981)	Crocidolite UICC	20	i.pl.	NR	21/39	54	***	
Osborne-Mendel – Stanton *et al.* (1981)	Crocidolite UICC	40	i.pl.	NR	14/29	48	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC	20	i.pl.	NR	35/41	85	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 1 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 2 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 4 h	20	i.pl.	NR	15/41	37	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 8 h	20	i.pl.	NR	13/42	31	***	
Fischer – Coffin *et al.* (1992)	Crocidolite UICC	0.5	i.pl.	0.04	65/144[d]	29	** [d]	
		2		0.16		13		
		4		0.32		50		
		8		0.65		67		
		16		1.3		58		
		32		2.6		54		
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.01	i.p.	0.0004	0/48	0	NS	
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.05	i.p.	0.002	8/32	25	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.5	i.p.	0.02	10/32	31	***	
Wistar – Pott *et al.* (1987)	Crocidolite South Africa	0.5	i.p.	0.05	18/32	56	***	
Wistar – Roller *et al.* (1996)	Crocidolite A	0.5	i.p.	0.042	25/32	78	***	All females
Wistar – Roller *et al.* (1996)	Crocidolite A	0.5	i.p.	0.042	32/48	67	***	All females
Wistar – Roller *et al.* (1996)	Crocidolite C	0.5	i.p.	0.042	20/39	51	***	
Wistar – Davis *et al.* (1985)	Tremolite, Korea	25	i.p.	NR	27/29	93	***	
Wistar – Roller *et al.* (1996)	Tremolite B	3.3	i.p.	0.057	9/40	23	***	
Wistar – Roller *et al.* (1996)	Tremolite B	15	i.p.	0.26	30/40	75	***	
Erionite	Erionite type							
Sprague-Dawley – Pott *et al.* (1987)	Karain	1.25	i.p.	NR	38/53	72	***	
Sprague-Dawley – Pott *et al.* (1987)	Karain	5	i.p.	NR	43/53	81	***	
Sprague-Dawley – Pott *et al.* (1987)	Karain	20	i.p.	G	37/53	70	***	
Fischer – Wagner *et al.* (1985)	Karain	20	i.pl.	NR	38/40	95	***	
Fischer – Wagner *et al.* (1985)	Oregon	20	i.pl.	NR	40/40	100	***	
Wistar – Pott *et al.* (1987)	Oregon	0.5	i.p.	0.02	15/31	48	***	
Wistar – Pott *et al.* (1987)	Oregon	2	i.p.	0.08	28/31	90	***	
Fischer – Wagner (1990)	Oregon	20	i.pl.	NR	30/32	94	***	
Fischer – Wagner (1990)	Oregon "short"	20	i.pl.	NR	0/32	0	NS	
Wistar – Davis *et al.* (1991b)	Oregon	0.005	i.p.	0.00025	0/48	0	NS	
		0.01		0.0005	4/48	8	*	
		0.05		0.0025	15/32	47	***	
		0.5		0.025	26/32	81	***	
		2.5		0.125	30/32	94	***	
		5		0.25	21/24	88	***	
		10		0.5	20/24	83	***	
		25		1.25	17/18	94	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Porton – Hill *et al.* (1990)	Oregon	0.1	i.pl.	NR	5/10	50	*	
		1		NR	9/10	90	***	
		10		NR	9/10	90	***	
		20		NR	8/10	80	***	
Wistar – Kleymenova *et al.* (1999)	Grusia mines	20	i.pl.	NR	39/40	98	?	
Fischer – Coffin *et al.* (1992)	Oregon "C"	0.5	i.pl.	NR	123/144[d]	79	***[d]	
		2		NR		87		
		4		NR		83		
		8		NR		84		
		16		NR		87		
		32		NR		91		
Fischer – Coffin *et al.* (1992)	Oregon "W"	0.5	i.pl.	NR	137/144[d]	100	***[d]	
		2		NR		92		
		4		NR		100		
		8		NR		91		
		16		NR		96		
		32		NR		92		
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.pl.	NR	35/40	88	***	
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.p.	NR	35/40	50	***	

[a] The fibre numbers mainly refer to fibres with a length greater than 5 µm
[b] n/z number of animals with serosal tumour (mesothelioma/sarcoma) / number of animals examined
[c] calculation of the statistical significance with the Fisher exact test, one-sided: *** $p < 0.001$; ** $p < 0.01$; * $p \leq 0.05$
[d] combined data of 6 groups
i.p., intrapleural; i.pl., intraperitoneal; NS, not significant; NR, not reported
From Pott & Roller (1993b)

Table 3.5 Carcinogenicity study of intrapleural application of asbestos fibres and other fibrous materials in female Osborne-Mendel rats (40 mg fibres per rat)

Fibrous dust (material)	No. of fibres [a] ($x10^6$) L > 8 µm D < 0.25 µm	Probability of pleural sarcomas [b]		Pleural sarcoma incidence [c]	
				n/z	%
Tremolite 1	55	100		22/28	79
Tremolite 2	28	100		21/28	75
Crocidolite 1	6500	94	± 6.0	18/27	67
Crocidolite 2	800	93	± 6.5	17/24	71
Crocidolite 3	4100	93	± 6.9	15/23	65
Amosite	140	93	± 7.1	14/25	56
Crocidolite 4	5400	86	± 9.0	15/24	63
Crocidolite 5 (UICC)	78	78	± 10.8	14/29	48
Crocidolite 6	1600	63	± 13.9	9/27	33
Crocidolite 7	18	56	± 11.7	11/26	42
Crocidolite 8	< 0.3[d]	53	± 12.9	8/25	32
Crocidolite 9	710	33	± 9.8	8/27	30
Crocidolite 10	49	37	± 13.5	6/29	21
Crocidolite 11	< 0.3[d]	19	± 8.5	4/29	14
Crocidolite 12	220	10	± 7.0	2/27	7
Talc 1	< 0.3[d]	7	± 6.9	1/26	4
Talc 3	< 0.3[d]	4	± 4.3	1/29	3
Talc 2	< 0.3[d]	4	± 3.8	1/30	3
Talc 4	< 0.3[d]	5	± 4.9	1/29	3
Crocidolite 13	< 0.3[d]	0		0/29	0
Talc 5	< 0.3[d]	0		0/30	0
Talc 6	80	0		0/30	0
Talc 7	< 0.3[d]	0		0/29	0

[a] Fibre numbers stated in original work as common logarithm.

[b] Calculation taking into account the different life spans (life table method).

[c] n/z = number of rats with pleural sarcomas/number of rats examined. Frequency of pleural sarcomas in female control rats: untreated, 3 animals out of 491 (0.6%); with non-carcinogenic lung implantates, 9 out of 441 (2.0%); with non-carcinogenic pleural implantates, 17 out of 615 (2.8%). [17 out of 615 against 3 out of 491, according to Fisher exact test $P < 0.01$]. All three control groups are brought together by Stanton *et al.* (1981) to 29 out of 1518 animals (1.9%); for this after application of the life table method a tumour probability of 7.7 ± 4.2% is indicated. [Without any reason being given it is concluded that the tumour probability in any one of the groups treated according to the life table method must exceed 30% to be "significantly" increased.] Significance limit for Fisher test in the case of 25 to 30 animals against 17 out of 615 control rats: approx. 12 to 13% tumour frequency. (The term "tumour frequency" is not to be equated with tumour probability according to the life table method. The "significance limit" of 30% mentioned by Stanton *et al.* (1981) refers to life table incidence or probability.

[d] The de-logarithmised fibre numbers with the above mentioned definition are between 0 and 0.3.

From Stanton *et al.* (1981)

8.0; 95%CI: 1.4–45.9). Lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher level of chrysotile asbestos fibres than lung tissue from control dogs (Glickman *et al.*, 1983).

3.8 Synthesis

Bronchial carcinomas and pleural mesotheliomas were observed in many experiments in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in tumour incidence at other sites. A special preparation of "long" crocidolite was more effective to induce lung tumours compared to the "short" UICC asbestos samples on the basis of administered dose in f/mL.

In one study in Syrian golden hamsters with three different concentrations of amosite, a significant increase in pleural mesothelioma incidence was observed, but no lung tumours were found.

After amosite exposure and crocidolite exposure by inhalation, 2/11 baboons and 3/21 baboons developed pleural mesothelioma, respectively.

In two studies in rats exposed to erionite, a significant increase in pleural mesothelioma incidence was observed. However, no lung tumours were found.

Samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelioma induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

Only a few studies have been carried out with intratracheal instillation of crocidolite in rats and hamsters. Malignant lung tumours were observed in rats, and pleural mesothelioma and malignant lung tumours were observed in hamsters.

Chrysolite, crocidolite and amosite were administered in the feed of rats and hamsters. No increase of the incidence of gastrointestinal tumours was observed in both species.

No chronic studies with vermiculite containing asbestos fibres or talc containing asbestos fibres could be identified.

4. Other Relevant Data

4.1 Toxicokinetics, deposition, clearance, and translocation in humans

4.1.1 Aerodynamic and anatomical factors

Inhalation is the most important route of exposure to mineral fibres, and is associated with the development of non-malignant diseases of the lungs and pleura, and malignant diseases arising in the lung, larynx, and pleural and peritoneal linings (IOM, 2006). The deposition of particles and fibres in the lungs is dependent on their aerodynamic diameter, which is a function of geometry, aspect ratio (IARC, 2002), and density (Bernstein *et al.*, 2005). Fibres can deposit by sedimentation, by impaction at bronchial bifurcations or by interception of the fibre tip with the bronchial wall. Smaller diameter fibres are likely to deposit in the alveoli (Bernstein *et al.*, 2005).

Particles and fibres can be cleared from the nasal and tracheobronchial regions by mucociliary transport (Lippmann *et al.*, 1980). Following deposition in the distal airways and alveoli, short fibres are removed more slowly following phagocytosis by alveolar macrophages. Fibre length is a limiting factor in macrophage-mediated clearance; fibres longer than the diameter of human alveolar macrophages (approximately 14–25 µm) are less likely to be cleared. Fibres may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites. Fibres that are not efficiently cleared or altered by physicochemical process (e.g. breakage, splitting, or

chemical modification) are termed biopersistent (Bernstein *et al.*, 2005). Chronic inhalation assays using man-made fibres in rodents have correlated fibre length and biopersistence with persistent inflammation, fibrosis, lung cancer, and malignant mesothelioma (Bernstein *et al.*, 2005). However, there are interspecies differences in alveolar deposition of inhaled particles and fibres that must be considered when extrapolating results of rodent inhalation studies to humans (IARC, 2002).

4.1.2 Biopersistence of asbestos and erionite fibres

Asbestos fibres and ferruginous bodies (described subsequently in Section 4.3.1) can be identified and quantified by tissue digestion of lung samples obtained by biopsy or at autopsy (Roggli, 1990). A variety of commercial and non-commercial asbestos fibres have been identified in residents older than 40 years of age living in an urban area with no history of occupational asbestos exposure (Churg & Warnock, 1980). These and other studies confirm that asbestos fibres are biopersistent and accumulate in lung tissue as well as lymph nodes (Dodson *et al.*, 1990; Dodson & Atkinson, 2006). Asbestos fibres have also been identified in the pleura following autopsy (Dodson *et al.*, 1990; Gibbs *et al.*, 1991; Suzuki & Yuen, 2001) and in the parietal pleural in samples collected during thoracoscopy (Boutin *et al.*, 1996). Roggli *et al.* (1980) also identified asbestos bodies in the larynx of asbestos workers at autopsy. Systemic translocation of asbestos fibres to distant organs has also been described in case reports; however, these reports should be evaluated with caution due to the numerous caveats in technical procedures used, comparison with an appropriate control population, and cross-contamination of tissue samples (Roggli, 2006). The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals (Hesterberg *et al.*, 1999; Mc Connell *et al.*, 1999; IOM, 2006; NIOSH, 2009).

Environmental exposure to erionite fibres is associated with diffuse malignant mesothelioma in three rural villages in the Cappadocia region of Turkey (Baris & Grandjean, 2006). Lung fibre digests obtained from humans in these villages showed elevated levels of erionite fibres, and ferruginous bodies surrounding erionite fibres were found in broncho-alveolar lavage fluid (Sébastien *et al.*, 1984; Dumortier *et al.*, 2001).

Talc particles have been found in the lungs at autopsy of both rural and urban residents as well as talc miners (IARC, 1987b, 2010). Talc particles are biopersistent in the lungs, and have been recovered in broncho-alveolar lavage fluid obtained from workers 21 years after cessation of occupational exposure (Dumortier *et al.*, 1989). Talc contaminated with asbestos has been linked to the development of lung cancer and malignant mesothelioma (IARC, 1987b).

The association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial (IARC, 2010, and this volume).

The biological plausibility for an association between asbestos and ovarian cancer derives in part from the finding of asbestos fibres in the ovaries of women with potential for exposure to asbestos. Thus, a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight), but only one of the 17

women without exposure had counts in that range (Heller *et al.*, 1996).

Further support for the biological plausibility of an association between asbestos exposure and ovarian cancer derives from an experimental study (Graham & Graham, 1967) that found that the intraperitoneal injection of tremolite asbestos into guinea-pigs and rabbits produced epithelial changes in the ovaries "similar to those seen in patients with early ovarian cancer".

[The Working Group noted that the histopathological diagnosis of ovarian carcinoma is difficult and requires the application of immunohistochemical techniques to distinguish between this cancer and peritoneal malignant mesothelioma. These techniques and the recognition of borderline ovarian tumours and variants of serosal tumours that arise in the pelvis of women were not applied in the Graham & Graham study in 1967. In addition, mesothelial hyperplasia occurs commonly in the pelvic region, and is not considered a preneoplastic lesion (NIOSH, 2009).]

4.2 Molecular pathogenesis of human cancers related to mineral dust exposure

Cancers develop in the upper and lower respiratory tract (carcinoma of the larynx and lungs), and in the pleural and peritoneal linings (diffuse malignant mesothelioma) after a long latent period up to 20–40 years following initial exposure to asbestos or erionite fibres (IARC, 1977; IOM, 2006). During the long latent period before the clinical diagnosis of cancer of the lung or of the larynx or diffuse malignant mesothelioma, multiple genetic and molecular alterations involving the activation of cell growth regulatory pathways, the mutation or amplification of oncogenes, and the inactivation of tumour–suppressor genes characterize specific histopathological types of these tumours that have been associated with exposure to mineral dust or fibres. Some of these molecular alterations have been linked to specific chemical carcinogens in tobacco smoke (Nelson & Kelsey, 2002), and additional alterations may arise secondarily due to chronic inflammation, genetic instability, or epigenetic changes that will be discussed in detail in Section 4.3.

Additional pathways related to resistance to apoptosis, acquired genetic instability, and angiogenesis are activated or upregulated during the later stages of tumour progression of lung cancer and diffuse malignant mesothelioma (Table 4.1; Table 4.2). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to asbestos fibres (NIOSH, 2009).

4.2.1 Cancer of the lung and of the larynx

Lung cancers are classified into two histological subtypes: small cell carcinoma and non-small cell carcinoma (Table 4.1). In non-small cell lung carcinoma, activating point mutations in the *K-RAS* oncogene have been linked to specific chemical carcinogens in tobacco smoke; Nelson *et al.* (1999) described more frequent *K-RAS* mutations in lung carcinomas in asbestos-exposed workers. Loss of heterozygosity and point mutations in the *p53* tumour-suppressor gene have also been linked with tobacco smoke carcinogens in cancer of the lung and of the larynx (Pfeifer *et al.*, 2002; NIOSH, 2009). These alterations have also been described in lung cancers in asbestos-exposed workers (Nymark *et al.*, 2008).

4.2.2 Diffuse malignant mesothelioma

Malignant tumours arising in the pleural or peritoneal linings (diffuse malignant mesothelioma) have no association with tobacco smoking, and are characterized by a different spectrum of molecular alterations (Table 4.2). In contrast with lung cancers associated with tobacco smoking and asbestos exposure, mutations in the *K-RAS*

Table 4.1 Some reported molecular alterations in bronchogenic carcinoma

Functional alterations	Gene target	Histological type of lung cancer	
		Small cell	Non-small cell
Autocrine growth stimulation	Growth factors and receptors	GRP/GRP receptor SCF/KIT	TGF-α/EGFR HGF/MET
Activation of oncogenes	*RAS* mutation	<1%	15–20%
	MYC overexpression	15–30%	5–10%
Inactivation of tumour-suppressor genes	*p53* mutation	~90%	~50%
	RB mutation	~90%	15–30%
	$p16^{INK4A}$ inactivation	0–10%	30–70%
	FHIT inactivation	~75%	50–75%
Resistance to apoptosis	*BCL2* expression	75–95%	10–35%
Genetic instability	Microsatellite instability	~35%	~22%

EGFR, epidermal growth factor receptor; FHIT, fragile histidine triad; GRP, gastrin-releasing peptide; HGF, hepatocyte growth factor; RB, retinoblastoma gene; SCF, stem cell factor; TGF-α, transforming growth factor-α.
From Sekido *et al.* (2001), Sato *et al.* (2007), Schwartz *et al.* (2007), NIOSH (2009)

oncogene or the *p53* tumour-suppressor gene are rare. The most frequent molecular alteration involves deletion or hypermethylation at the *CDKN2A/ARF* locus on chromosome 9p21 which contains three tumour-suppressor genes: *p15*, $p16^{INK4A}$, and $p14^{ARF}$ (Murthy & Testa, 1999). Additional molecular alterations include hypermethylation and silencing of the *RASSFIA* and *GPC3* tumour-suppressor genes, and inactivation of the *NF2* tumour-suppressor gene (Apostolou *et al.*, 2006; Murthy *et al.*, 2000).

Comparative genomic hydrizidation, gene expression profiling, and proteomics have been used to identify specific diagnostic and prognostic biomarkers for diffuse malignant mesothelioma (Wali *et al.*, 2005; Greillier *et al.*, 2008). The most promising outcome of these global screening strategies is the identification of two potential serum or pleural fluid biomarkers that may provide early diagnosis of malignant pleural mesothelioma: osteopontin (Pass *et al.*, 2005), and soluble mesothelin-related protein (Robinson *et al.*, 2005). Both of these markers have been shown to be elevated in most patients diagnosed with diffused malignant mesothelioma, but are not entirely specific for these cancers (Greillier *et al.*, 2008). No gene expression signature can be attributed directly to asbestos exposure, and these studies show variable gene expression patterns resulting from limited stability of RNA, contamination of tumour samples with host cells, and use of different microarray platforms (López-Ríos *et al.*, 2006).

In addition to the genetic and chromosomal alterations that have been identified in diffuse malignant mesothelioma (Table 4.2), epigenetic alterations characterized by altered patterns of DNA methylation have been described (Toyooka *et al.*, 2001; Tsou *et al.*, 2005). Overall, human tumours have been characterized by global hypomethylation associated with hypermethylation of CpG islands in the promoter regions of tumour-suppressor genes leading to their inactivation. These alterations in DNA methylation are the most common molecular or genetic lesion in human cancer (Esteller, 2005). Recent comprehensive analyses of epigenetic profiles of 158 patients with malignant pleural mesotheliomas and 18 normal pleural samples using 803 cancer-related genes revealed classes of methylation profiles in malignant mesothelioma that were associated with asbestos lung burden and survival (Christensen *et al.*, 2009). Other data confirmed hypermethylation of cell-cycle

Table 4.2 Some reported molecular alterations in diffuse malignant mesothelioma

Function	Gene target	Alteration
Autocrine growth stimulation	Growth factors and receptors	HGF/MET upregulation EGFR upregulation PDGF upregulation IGF-1 upregulation
Tumour-suppressor genes	*p15, p16^{INK4A}, p14^{ARF}*	Inactivation or deletion
	Neurofibromin 2	*NF2* deletions, mutations
	RASSF1A, GPC3	Hypermethylation
Angiogenesis	VEGF	Upregulation
Apoptosis	*AKT*	Constitutive activation
	BCL-X	Upregulation

EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; PDGF, platelet-derived growth factor; RASSF1A, Ras-association domain family 1; VEGF, vascular endothelial growth factor

From Murthy & Testa (1999), Altomare *et al.* (2005), Catalano *et al.* (2005), Kratzke & Gazdar (2005), Cacciotti *et al.* (2006), NIOSH (2009)

regulatory genes as well as inflammation-associated genes and apoptosis-related genes (Tsou *et al.*, 2007; Christensen *et al.*, 2008). Christensen *et al.* (2009) hypothesized that hypermethylation of specific genes confers a selective survival advantage to preneoplastic mesothelial cells in a microenvironment of persistent tissue injury and/or oxidative stress associated with exposure to asbestos fibres.

In summary, these new genomic and proteomics approaches offer promise for the discovery of novel biomarkers associated with the development of diffuse malignant mesothelioma following exposure to asbestos or erionite. No specific marker is yet available to identify those cancers.

4.3 Mechanisms of carcinogenesis

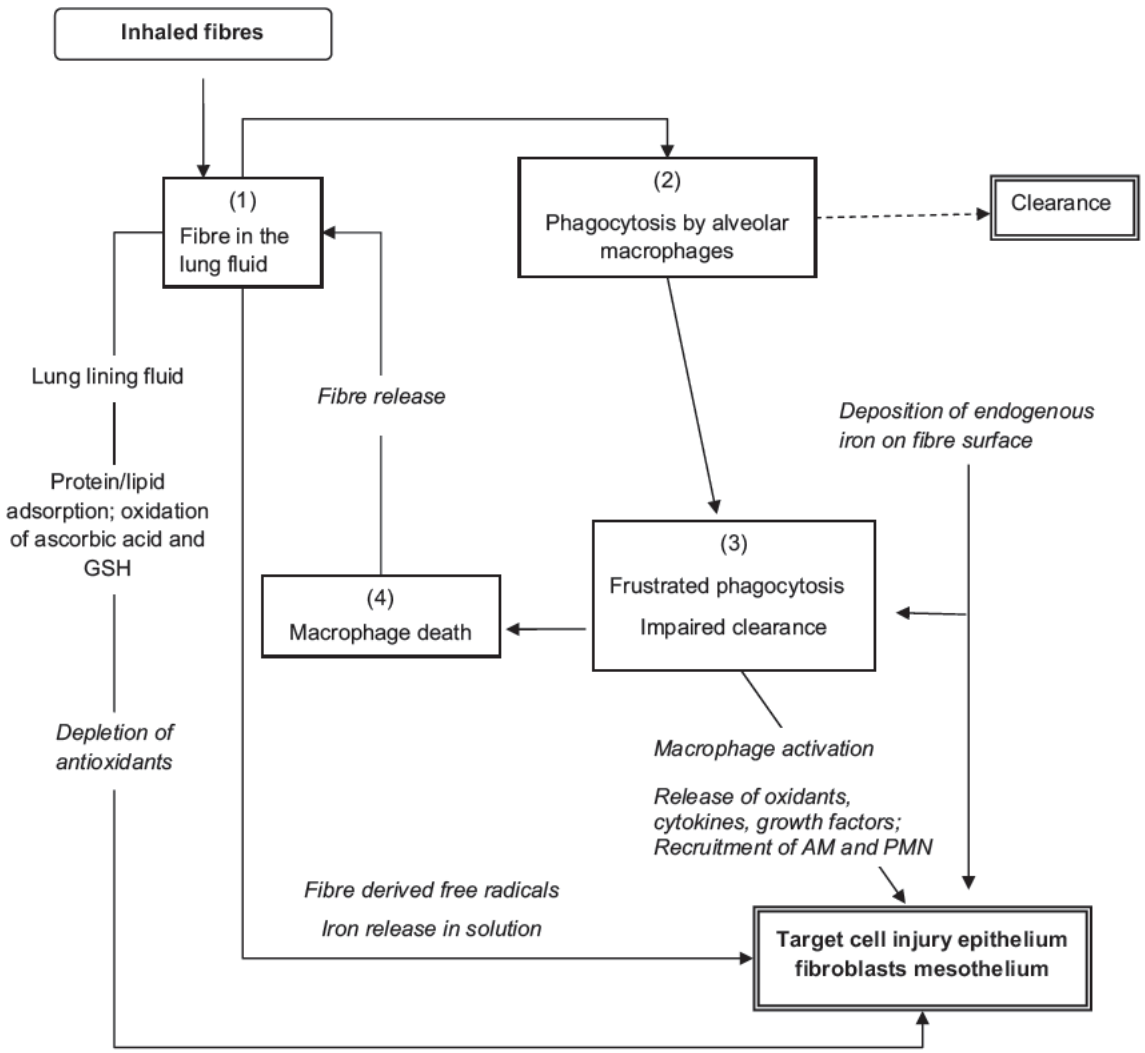
4.3.1 Physicochemical properties of mineral fibres associated with toxicity

Asbestos are natural fibrous silicates, with similar chemical composition (silica framework includes various metal cations, typically Mg^{2+}, Ca^{2+}, $Fe^{2+/3+}$, Na^{+}) mostly differing in the crystallographic constraints that yield the fibrous habit. They are poorly soluble minerals which only undergo selective leaching and incongruent dissolution. Erionite is a zeolite, which often crystallizes in thin long fibres. Major determinants of toxicity are form and size of the fibres, surface chemistry, and biopersistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure (Fubini, 1997; Bernstein *et al.*, 2005; Fubini & Fenoglio, 2007; Sanchez *et al.*, 2009; Fig. 4.1).

(a) Crystal structure

Asbestos minerals can be divided into two groups: serpentine asbestos (chrysotile [$Mg_3Si_2O_5(OH)_4$]), and amphibole asbestos (crocidolite [$Na_2(Mg,Fe^{2+})_3Fe_2^{3+}Si_8O_{22}(OH)_2$], amosite [$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$], tremolite [$Ca_2Mg_5Si_8O_{22}(OH)_2$], actinolite [$Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$], and anthophyllite [$Mg_7Si_8O_{22}(OH)_2$]). Formulae reported are ideal and are always significantly modified in nature by the occurrence of several substituting cations (e.g. $Fe^{2+/3+}$, Al^{3+}, Na^{+}). The crystal structure of chrysotile results from the association of a tetrahedral silicate sheet of composition $(Si_2O_5)_n^{2n-}$ with an octahedral brucite-like sheet of composition $[Mg_3O_2(OH)_4]_n^{2n+}$, in which iron substitutes for magnesium. The two sheets are bonded to form a 1:1 layer silicate; a slight misfit between the sheets causes curling to form

Fig. 4.1 Physicochemical properties involved in the biological activity of asbestos fibres



AMs, alveolar macrophages; GSH, glutathione; PMNs, polymorphonuclear neutrophils
Adapted from Fubini & Otero Areán (1999), Fubini & Fenoglio (2007)

concentric cylinders, with the brucite-like layer on the outside. Van der Waals interparticle forces hold together fibrils into the actual fibre so that, when chrysotile breaks up, a large number of smaller fibres or fibrils are generated (Fubini & Otero Areán, 1999).

Amphiboles have an intrinsically elongated crystal structure which breaks up along planes within the crystal structure itself into progressively smaller fragments that generally retain a fibrous aspect. This structure can be described in terms of a basic structural unit formed by a double tetrahedral chain (corner-linked SiO_4 tetrahedra) of composition $(Si_4O_{11})_n^{6n-}$. These silicate double-chains share oxygen atoms with alternate layers of edge-sharing MO_6 octahedra, where M stands for a variety of cations: mostly Na^+, Mg^{2+}, Ca^{2+}, Fe^{2+}, or Fe^{3+} (Fubini & Otero Areán, 1999).

(b) Form and size

The pathogenic potential of asbestos depends upon its aspect ratio and fibre size. Fibre size affects respirability (respiratory zone falls off above aerodynamic diameters of 5 µm) and clearance by alveolar macrophages (section 4.1.1) (Donaldson & Tran, 2004). Short fibres are cleared more efficiently than longer ones, which undergo frustrated phagocytosis by macrophages. Short amosite fibres obtained by grinding long ones are less inflammogenic (Donaldson *et al.*, 1992), induce fewer chromosomal aberrations (Donaldson & Golyasnya, 1995), and reduce the inhibition of the pentose phosphate pathway (Riganti *et al.*, 2003). In-vitro genotoxicity studies demonstrated that both short and intermediate chrysotile asbestos fibres induced micronuclei formation and sister chromatid exchange in Chinese hamster lung cells. Intermediate fibres were more active than short fibres even when followed by treatment with dipalmitoyl lecithin, a principal constituent of pulmonary surfactant (Lu *et al.*, 1994). Long fibres but not short fibres of amosite asbestos, opsonized with rat immunoglobin, were shown to induce a dramatic enhancement of superoxide anions in macrophages isolated from rat lung (Hill *et al.*, 1995). Asbestos bodies are formed mostly on fibres longer than 20 µm (Roggli, 2004).

The role of the aspect ratio and size appears to be different for the three major asbestos-related diseases: i) asbestosis was reported as most closely associated with the surface area of retained fibres (NIOSH, 2009) although fibrosis also correlates with fibres > 2 µm long (Dodson *et al.*, 2003); ii) mesothelioma is better related to the numbers of fibres longer than about 5 µm and thinner than about 0.1 µm; and iii) lung cancer with fibres longer than about 10 µm and thicker than about 0.15 µm (NIOSH, 2009). Several studies, however, report the presence of very short fibres in lung and pleural tissue from patients with malignant mesothelioma (Dodson *et al.*, 2003; Dodson *et al.*, 2005; Suzuki *et al.*, 2005; Dodson *et al.*, 2007), suggesting caution to exclude short fibres (< 5 µm) in the development of asbestos-related diseases (Dodson *et al.*, 2003).

(c) Surface reactivity

In the last few decades, it has been accepted that, in addition to fibrous habit, surface reactivity also plays a role in the pathogenic effects of amphibole and chrysotile asbestos. The potential to release free radicals, among various other features, is considered the major determinant of the pathogenic response.

(i) Free-radical generation

Three different mechanisms of free-radical generation may take place at the surface of asbestos fibres, each one triggered by a different kind of active surface site: i) Fenton chemistry (yielding with H_2O_2 the generation of highly reactive hydroxyl radicals HO•); ii) Haber–Weiss cycle (in the absence of H_2O_2 and Fe(II), endogenous reductants allow progressive reduction of atmospheric oxygen to HO•); iii) homolytic

rupture of a carbon-hydrogen bond in biomolecules, with generation of carbon-centred radicals in the target molecule (peptides, proteins, etc.) (Hardy & Aust, 1995; Fubini & Otero Areán, 1999; Kamp & Weitzman, 1999).

Mechanism i) is relevant only in cellular compartments where H_2O_2 is present (i.e. phagolysosomal environment in macrophages), while Mechanisms ii) and iii)_may occur ubiquitously once fibres are inhaled. All mechanisms require the presence of iron ions. One stoichiometric chrysotile prepared by chemical synthesis, thus fully iron-free, was not active in free-radical generation (cell-free tests), did not induce lipid peroxidation, nor inhibit the pentose phosphate pathway in human lung epithelial cells, which is the opposite to what is found in natural specimens (Gazzano *et al.*, 2005). When loaded with less than 1 wt.% of Fe^{3+} the synthetic chrysotile also became active (Gazzano *et al.*, 2007). Asbestos fibres deprived of iron (following treatments with chelators) do not generate hydroxyl radicals (Fubini *et al.*, 1995) or damage DNA, and are less potent in causing lipid peroxidation *in vitro* (Hardy & Aust, 1995). However, not all iron ions are equally reactive in free-radical generation, depending upon their coordination and oxidation state (Shukla *et al.*, 2003; Bernstein *et al.*, 2005). Fe (II) is active even in trace amounts (Fubini *et al.*, 1995). Furthermore, Mechanism 3 requires isolated and poorly coordinated iron ions (Martra *et al.*, 2003; Turci *et al.*, 2007). The surface sites involved in this reaction are oxidized and become inactive following thermal treatments: amphibole asbestos fibres heated up to 400°C in air (Tomatis *et al.*, 2002) lose their potential in generating carboxyl radicals, but retain the reactivity for hydroxyl radicals, most likely through Mechanism 2, as long as their crystal structure is preserved. Conversely, the reduction of ferric into ferrous ions increases the radical activity (Gulumian *et al.*, 1993a). The radical yield appears unrelated to the total amount of iron (Gulumian *et al.*, 1993b), because chrysotile shows a similar behaviour to crocidolite in cell-free tests despite the lower content of iron (3–6% versus 27%). Iron oxides (magnetite, haematite) are unable to produce radical species, whereas model solids, e.g zeolites enriched with small amount of iron but with ions poorly coordinated and mostly in low valence state, are very reactive, particularly in hydrogen abstraction (Fubini *et al.*, 1995).

Iron-derived free radicals are believed to produce a variety of cell effects including lipid peroxidation (Ghio *et al.*, 1998; Gulumian, 1999), DNA oxidation (Aust & Eveleigh, 1999), TNF-release and cell apoptosis (Upadhyay & Kamp, 2003), adhesion (Churg *et al.*, 1998), and an increase of fibre uptake by epithelial cells (Hobson *et al.*, 1990).

(ii) Iron bioavailability and biodeposition

Iron can be removed from asbestos fibres by intracellular chelators. If iron is mobilized from low–molecular-weight chelators, e.g. citrate, redox activity may be altered. The chelator–iron complex can diffuse throughout the cell, and catalyse the formation of hydroxyl radicals. Mobilization of iron was shown to correlate with DNA strand breaks and with DNA oxidation induced by crocidolite, amosite, and chrysotile (Hardy & Aust, 1995). In human lung epithelial and pleural mesothelial cells, the extent of iron mobilization was also related to the inactivation of epidermal growth factor receptor (EGFR/ErbB1), a step in the pathway leading to apoptosis (Baldys & Aust, 2005).

Mineral fibres may also acquire iron which, under certain conditions, may modify their reactivity. Erionite (Dogan *et al.*, 2008) is able to bind both ferrous (through ion exchange) and ferric ions (through a precipitation or crystallization process). After ferrous-binding, erionite acquires the ability to generate hydroxyl radicals, and to catalyse DNA damage (DNA single-strand breaks); and after ferric-binding, the reactivity is acquired only in the presence of a reductant

(Hardy & Aust, 1995; Fach *et al.*, 2003; Ruda & Dutta, 2005). During their residence in the lung, asbestos fibres, like erionite fibres, acquire iron via a complex mechanism that may originate from the adsorption and disruption of ferritin, eventually yielding ferruginous bodies. These so-called asbestos bodies are preferentially formed onto long amphibole fibres but have also been found onto chrysotile fibres (Roggli, 2004). Although the presence of asbestos bodies in asbestos-related diseases is well documented, their biological role is still controversial. Iron deposition was thought to protect cells (Ghio *et al.*, 1997), but, deposited iron may become redox-active, thus enhancing the catalytic potential of the fibres (Ghio *et al.*, 2004). Asbestos bodies with amosite cores caused DNA single-strand breaks (Lund *et al.*, 1994); and increased radical damage to DNA was reported for ferritin-covered amosite in the presence of ascorbic acid (Otero-Areán *et al.*, 1999). Asbestos fibres might also disrupt normal iron homeostasis in the host by mobilizing and accumulating this metal (Ghio *et al.*, 2008).

Binding Fe (II) from solution increases iron mobilization from crocidolite by chelators, and induces DNA single-strand breaks. Increased lipid peroxidation and release of leukotriene B4 is found in alveolar macrophages from rats treated with Fe (III)-loaded crocidolite, and Fe (III)-loaded crocidolite fibres induce more DNA single-strand breaks *in vitro* than do untreated crocidolite fibres (Ghio *et al.*, 1992).

It was suggested that crocidolite stimulates inductible nitric oxide synthase by decreasing iron bioavailability (Aldieri *et al.*, 2001).

(d) Biopersistence, biodurability, and ecopersistence

The residence time in the lung depends upon both the clearance mechanisms and physico-chemical processes taking place. Clearance mechanisms are mainly related to the shape and size of the particle, whereas chemical composition, surface area, and structural parameters mainly affect leaching, dissolution, and breakage.

Selective leaching is more pronounced for serpentine asbestos than for amphiboles, which have no leachable "weak points" in their structure. Selective leaching of chrysotile occurs under strong acidic or chelating conditions, resulting in removal of Mg^{2+} ions. The kinetics vary according to the origin of the material, mechanical treatments, and associated contaminants, e.g. presence of nemalite (fibrous brucite) (Morgan, 1997). Chrysotile may lose magnesium *in vivo*, following phagocytosis by alveolar macrophages. The biological potential of magnesium-depleted chrysotile is greatly decreased (Langer & Nolan, 1994; Gulumian, 2005). Furthermore, leached fibres undergo breakage into shorter fibres, which may be cleared more readily from the lung. This accounts for the relatively low biopersistence of chrysotile compared to the amphiboles. The lungs of some chrysotile workers at autopsy contain low levels of chrysotile but substantial numbers of tremolite fibres, which is present in some chrysotile-bearing ores. For this reason, tremolite has been suggested to contribute to the carcinogenic effects seen in chrysotile miners (McDonald *et al.*, 1997; McDonald & McDonald, 1997; McDonald, 1998). Other asbestiform minerals may be associated with chrysotile, and, in some cases, modulate its toxicity, depending upon their amount and physicochemical characteristics. Balangeroite, occasionally intergrows with chrysotile (up to 5%) in the Balangero mine (Italy) and its sourroundings. Balangeroite fibres have a different structure from amphiboles, and are poorly eco- and bio-durable (Favero-Longo *et al.*, 2009; Turci *et al.*, 2009). Balangeroite may contribute to the overall toxicity of chrysotile, but it cannot be compared to tremolite nor considered to be solely responsible for the excess of mesothelioma found in Balangero (Mirabelli *et al.*, 2008).

In the natural environment, weathering processes carried out by micro-organisms

may induce chrysotile-leaching, contributing to its bioattenuation (Favero-Longo *et al.*, 2005). However, the dissolution of chrysotile is very low, because any breakdown of the silica framework takes place at a slow rate (Hume & Rimstidt, 1992), and is limited to a few layers in mild conditions (Gronow, 1987). Even in a strong acidic environment, the final product still retains a fibrous aspect at the nanoscale which is devoid of cations (Wypych *et al.*, 2005).

4.3.2 Direct genotoxicity

Mineral fibres may directly induce genotoxicity by catalysing the generation of reactive oxygen species resulting in oxidized DNA bases and DNA strand breaks that can produce gene mutations if not adequately repaired (IOM, 2006). Both asbestos and erionite fibres can induce DNA damage mediated by reactive oxygen species. Asbestos fibres have also been shown to physically interfere with the mitotic apparatus, which may result in aneuploidy or polyploidy, and specific chromosomal alterations characteristic of asbestos-related cancer (Jaurand, 1996).

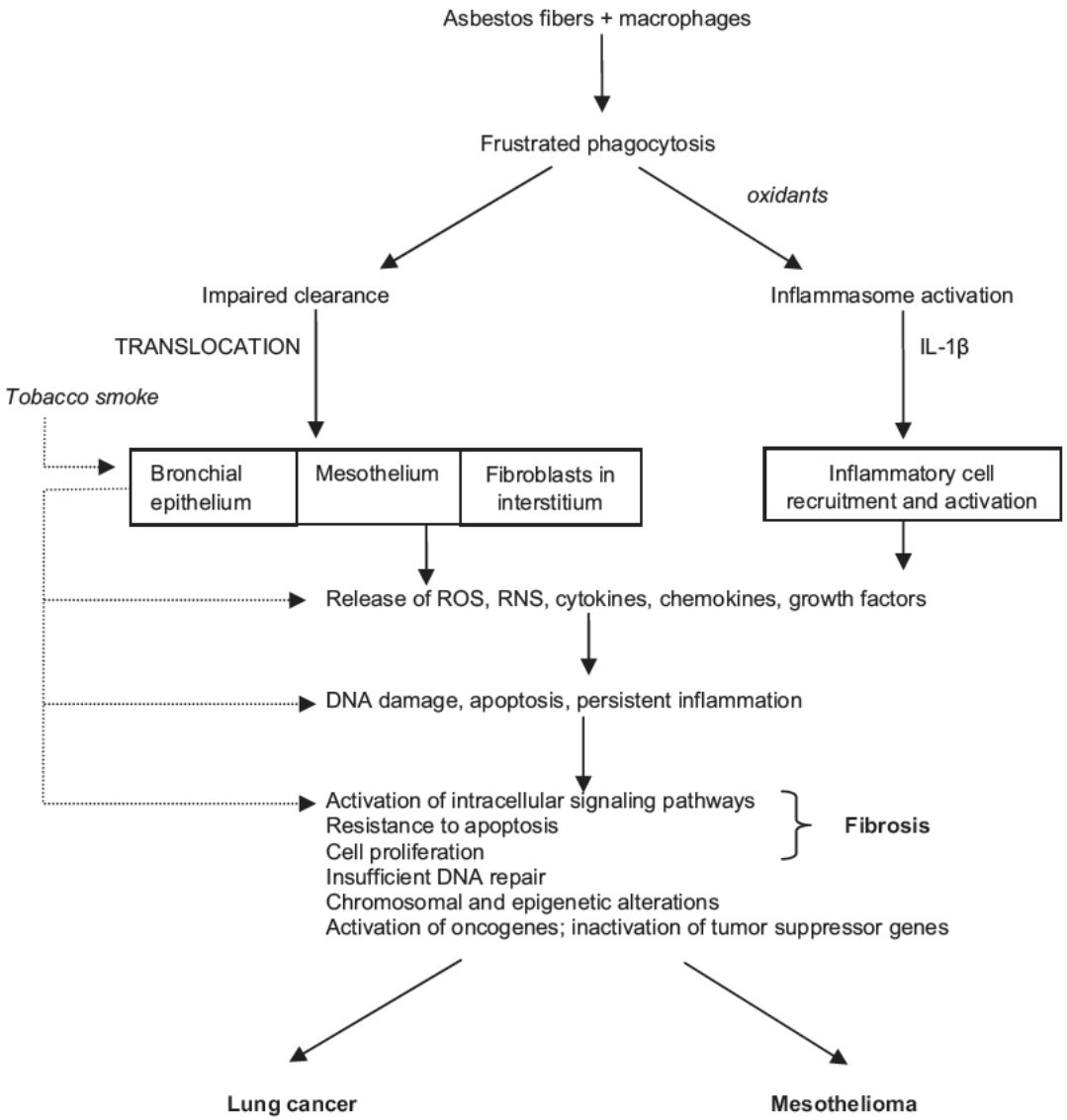
In addition to direct clastogenic and aneuploidogenic activities that may be induced following the translocation of asbestos fibres to target cell populations in the lungs, persistent inflammation and macrophage activation can secondarily generate additional reactive oxygen species, and reactive nitrogen species that can indirectly induce genotoxicity in addition to activation of intracellular signalling pathways, stimulation of cell proliferation and survival, and induction of epigenetic alterations (Fig. 4.2).

4.3.3 Indirect mechanisms

Asbestos fibres have unique and potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (asbestosis), and lung cancer (Shukla *et al.*, 2003). Macrophages express a variety of cell-surface receptors that bind to mineral fibres leading to phagocytosis, macrophage apoptosis, or macrophage activation. Receptors expressed by macrophages and other target cells in the lung that bind mineral fibres include MARCO, a scavenger receptor class A, and integrin receptors (Boylan *et al.*, 1995; Gordon *et al.*, 2002; Arredouani *et al.*, 2005). Macrophage apoptosis has also been postulated to contribute to an increased incidence of autoimmune diseases in residents in Libby, Montana, USA, who are exposed to vermiculite contaminated with amphibole asbestos fibres (Noonan *et al.*, 2006; Blake *et al.*, 2008).

Phagocytosis of asbestos fibres leads to the excess generation of reactive oxygen and nitrogen species by both direct (described in Sections 4.3.1 and 4.3.2), and indirect mechanisms (Manning *et al.*, 2002). Alveolar macrophages phagocytize particulate materials and micro-organisms leading to assembly of NADPH oxidase in the phagolysosomal membrane that generates reactive oxygen species, which are potent antimicrobial agents. Asbestos fibres have elevated surface reactivity and redox-active iron that can generate hydroxyl radicals leading to lipid peroxidation, protein oxidation, and DNA damage resulting in lung injury that is amplified by persistent inflammation (Fig. 4.1 and 4.2). Recent investigations in genetically engineered mice have provided evidence for a key role of the NALP3 inflammasome as an intracellular sensor of the initial interactions between asbestos fibres and other crystals such as monosodium urate with macrophages (Yu & Finlay, 2008). The NALP3 inflammasome activates caspase-1 that cleaves IL-1β precursor to active IL-1β that is rapidly secreted (Cassel *et al.*, 2008; Dostert *et al.*, 2008). This cytokine then triggers the recruitment and activation of additional inflammatory cells and the release of additional cytokines including TNF-α, IL-6, and IL-8 that perpetuate a prolonged inflammatory response to these biopersistent mineral dusts (Shukla *et al.*, 2003).

Fig. 4.2 Proposed mechanism for the carcinogenicity of asbestos fibres



IL-1β, interleukin -1β; RNS, reactive nitrogen species; ROS, reactive oxygen species.
Adapted from Shukla *et al.* (2003), Kane (2006), Nymark *et al.* (2008)

The generation of reactive oxygen species by asbestos fibres has also been associated with inducing apoptosis in mesothelial cells (Broaddus *et al.*, 1996), and alveolar epithelial cells (Aljandali *et al.*, 2001).

Asbestos fibres have been shown to contribute to the transformation of a variety of target cells from different species *in vitro*, and to induce lung tumours and malignant pleural mesothelioma in rodents following chronic inhalation (Bernstein *et al.*, 2005). There are important species differences in the induction of asbestos-related cancers: rats are more susceptible to the induction of lung cancer, and hamsters are resistant to the induction of lung cancer but more susceptible to the development of malignant pleural mesothelioma (IARC, 2002). Subchronic inhalation studies using refractory ceramic fibres (RCF-1) suggest that the increased susceptibility of hamsters to developing malignant pleural mesothelioma may be related to greater translocation and accumulation of fibres in the pleural space, and an increased mesothelial cell proliferation in hamsters compared to rats (Gelzleichter *et al.*, 1999). There are serious limitations in extrapolating these species differences to humans. First, most human lung cancers, even in asbestos-exposed individuals, are confounded by tobacco smoke that has potent independent genotoxic effects as reviewed later in Section 4.4.1. Second, diffuse malignant mesothelioma in humans is usually diagnosed at an advanced stage, and there are no reliable premalignant changes or biomarkers that may provide clues about the molecular pathogenesis of mesothelioma associated with exposure to asbestos or erionite fibres (NIOSH, 2009).

A unifying mechanism based on the experimental in-vitro cellular and in-vivo rodent models is proposed in Fig. 4.2.

Recent biochemical studies have confirmed that oxidative damage to cytosine is a plausible biological mechanism leading to epigenetic alterations and development of cancer in association with persistent inflammation (Valinluck & Sowers, 2007). Neutrophils and macrophages are the source of reactive oxygen and nitrogen species triggered by phagocytosis of crystalline silica (quartz) or asbestos fibres. In addition, myeloperoxidase catalyses the formation of hypochlorous acid (HOCl) in neutrophils, and a specific peroxidase catalyses the formation of hypobromous acid (HOBr) in eosinophils (Babior, 2000). The formation of 8-oxoguanine, 5-hydroxymethylcytosine, or 5-hydroxycytosine interferes with DNA methylation and binding of methyl-CpG binding domains (MBDs). In contrast, chlorination or bromination of cytosine mimics 5-methylcytosine and induces heritable DNA methylation at previously unmethylated sites. Halogenated cytosines are also recognized by MBDs to facilitate chromatin remodelling. However, these modified bases are not recognized by DNA glycosylase, and are not repaired (Valinluck & Sowers, 2007).

This hypothesis linking heritable alterations in patterns of cytosine methylation with endogenous sources of oxidants released from inflammatory cells is a plausible explanation for the development of lung cancer and diffuse malignant mesothelioma associated with exposure to mineral fibres. Elevated neutrophils and eosinophils have been found in the pleural space following the inhalation of refractory ceramic fibres by hamsters and rats (Gelzleichter *et al.*, 1999). Furthermore, myeloperoxidase activity has been detected in rodent lungs following exposure to asbestos fibres, whereas a decreased lung inflammation was observed in asbestos-exposed myeloperoxidase-null mice (Haegens *et al.*, 2005). This indirect mechanism secondary to persistent inflammation may be responsible for altered epigenetic methylation profiles, which are characteristic of human malignant pleural mesotheliomas (Christensen *et al.*, 2009).

4.4 Susceptible populations

Both exogenous environmental and occupational exposures and endogenous factors including genetic susceptibility contribute to the development of lung cancer (NIOSH, 2009) and diffuse malignant mesothelioma (Weiner & Neragi-Miandoab, 2009). The best example of an exogenous exposure that is a major cofactor with asbestos fibres in the development of cancer of the larynx and of the lung is tobacco smoking (Table 4.3; Table 4.4; IARC, 2004; IOM, 2006). Additional environmental and occupational exposures are also risk factors for cancer of the larynx (Table 4.3) and of the lung (Table 4.4); these exposures are potential confounders in human epidemiological studies (IOM, 2006). Specific examples of these cofactors and other environmental and occupational exposures will be described in relationship to mechanisms of these cancers associated with mineral dust exposures.

4.4.1 *Other risk factors for cancer of the lung and of the larynx, and diffuse malignant mesothelioma*

(a) Tobacco smoke

Co-exposure to tobacco smoke and asbestos fibres is at least additive and possibly multiplicative in the development of lung cancer (Vainio & Boffetta, 1994). The inhalation of tobacco smoke (Walser *et al.*, 2008) as well as mineral fibres is associated with excess generation of reactive oxygen and nitrogen metabolites, cell injury and apoptosis, and persistent lung inflammation (Shukla *et al.*, 2003; IARC, 2004). Excess oxidant generation has been shown to enhance the penetration of asbestos fibres into respiratory epithelial cells, and to impair fibre clearance (McFadden *et al.*, 1986; Churg *et al.*, 1989), as well as altering the metabolism and detoxification of tobacco smoke carcinogens (Nymark *et al.*, 2008). Asbestos fibres can also adsorb tobacco smoke carcinogens and metals and facilitate their transport into the lungs (IOM, 2006). Asbestos fibres have also been shown to activate growth-factor receptors and cell-signalling pathways that stimulate cell proliferation and promote cell survival (Albrecht *et al.*, 2004). In summary, co-exposures to tobacco smoke and mineral fibres can amplify acquired genetic mutations induced by tobacco smoke carcinogens, and amplify cell proliferation in response to tissue injury leading to an increased risk for the development of cancer of the larynx and of the lung (Nymark *et al.*, 2008).

Table 4.3 Risk factors for the development of cancer of the larynx

Exposure	Reference
Active tobacco smoking	IARC (1986, 2004, 2012d)
Alcohol	IARC (1988, 2010, 2012d)
Mustard gas	IARC (1987a, 2012e)
Inorganic acid mists containing sulfuric acid	IARC (1992, 2012e)
Asbestos fibres	IOM (2006), IARC (2012b)
Human papilloma virus (HPV): types 6, 11, 16, 18 limited evidence	IARC (2007, 2012c)

Compiled by the Working Group

(b) Other occupational and environmental exposures

Alcohol and occupational exposure to irritants (Table 4.3) also contribute to the development of cancer of the larynx. These irritants, similar to inhalation of tobacco smoke, can cause repeated episodes of injury to the respiratory epithelium, resulting in metaplasia and dysplasia (Olshan, 2006); these preneoplastic lesions may then acquire additional molecular alterations and progress towards the development of invasive lung or laryngeal carcinoma. Other occupational exposures responsible for the development of lung cancer include direct-acting carcinogens such as ionizing radiation (IARC, 2000, 2012a), and metals (reviewed in IARC, 2012b).

Table 4.4 Risk factors for the development of cancer of the lung

Exposure	Reference
Active and passive tobacco smoking	IARC (2004, 2012d)
Ionizing radiation	IARC (2000, 2012a)
Respirable dusts and fibres:	
Asbestos	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Crystalline silica (quartz)	IARC (1997, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), McDonald *et al.* (2004), IARC (2012b)
Bis(chloromethyl)ether and chloromethyl methyl ether	IARC (1987a, 2012e)
Arsenic and arsenic compounds	IARC (1987a, 2012b)
Beryllium	IARC (1993, 2012b)
Cadmium and cadmium compounds	IARC (1993, 2012b)
Hexavalent chromium	IARC (1990, 2012b)
Nickel sulfate, oxides, and sulfides	IARC (1990, 2012b)
Soots	IARC (1985, 1987a, 2012e)

Compiled by the Working Group

The strongest risk factors associated with the development of diffuse malignant mesothelioma include environmental or occupational exposures to erionite, asbestos fibres, and talc or vermiculite contaminated with asbestos fibres (Table 4.5; NIOSH, 2009). It is unknown whether the carcinogenic effects of exposure to mixed dusts contaminated with asbestos fibres can be entirely attributed to the asbestos fibres or whether co-exposure to talc or vermiculite dusts potentiates the retention and/or biological activity of asbestos fibres *in vivo* (Davis, 1996). The occurrence of talc pneumoconiosis and its relationship to other mineral dust contaminants including quartz and tremolite was recently reviewed (IARC, 2010). In-vitro assays of talc cytotoxicity were also summarized (IARC, 2010). No experimental studies have been published assessing the cytotoxicity of vermiculite contaminated with asbestos fibres. A sample of the mixture of amphibole fibres associated with Libby vermiculite ore has been shown to induce cytotoxicity and oxidative stress in macrophages *in vitro* (Blake *et al.*, 2007).

(c) *SV40 and HPV viruses*

Two human DNA tumour viruses have been linked with an increased risk for cancer of the larynx (Table 4.3; high-risk subtypes of human papillomavirus (HPV)) and diffuse malignant mesothelioma (Table 4.5; Simian virus 40 (SV40)).

The evidence for HPV 16 in the development of cancer of the larynx has been evaluated as limited, although it has been implicated as an independent risk factor in the development of other squamous cell carcinomas arising in the head and neck region (IARC, 2007, 2012c).

The association between exposure to SV40 and asbestos fibres in the development of diffuse malignant mesothelioma is highly controversial (Butel & Lednicky, 1999; Gazdar *et al.*, 2002; Shah, 2004; IOM, 2006). SV40 is not an essential cofactor for the development of mesothelioma; for example, residents of the Cappadocian villages in Turkey have a very high risk for diffuse malignant mesothelioma but do not have evidence of SV40 exposure (Dogan *et al.*, 2006). Although there are several in-vitro mechanistic

Table 4.5 Risk factors for the development of diffuse malignant mesothelioma

Exposure	Reference
Asbestos fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), IARC (1987a, 2012e), McDonald *et al.* (2004)
Thorotrast	IARC (2001, 2012a)

Compiled by the Working Group

studies that support a role for SV40 viral oncogenes in the transformation of mesothelial cells, the human epidemiological evidence is inconclusive to support a causal association (Weiner & Neragi-Miandoab, 2009).

4.4.2 Genetic susceptibility

(a) Cancer of the lung

Tobacco smoke is the major cause of cancer of the lung; however, only a few rare hereditary syndromes are associated with an increased risk of lung, as well as other cancers: Bloom syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma (Lindor *et al.*, 2006). Other genetic polymorphisms in genes related to the metabolism and detoxification of tobacco smoke carcinogens, antioxidant defenses, and DNA repair have been suggested as predisposing factors for the development of lung cancer, although individually they contribute minimally to an increased risk (IOM, 2006). Attempts have been made to identify genetic polymorphisms in enzymes involved in xenobiotic metabolism and antioxidant defense that increase the risk for asbestos-related lung cancer; however, no consistent associations have been found (Nymark *et al.*, 2008).

(b) Diffuse malignant mesothelioma

With the exception of certain populations who have been exposed environmentally to asbestos or erionite fibres since birth (NIOSH, 2009), the development of diffuse malignant mesothelioma even in occupationally exposed workers is less common than the development of lung cancer (Nymark *et al.*, 2008). This observation has led to the hypothesis that there may be a genetic predisposition to the development of diffuse malignant mesothelioma following exposure to asbestos or erionite fibres. Isolated case reports provide examples of diffuse malignant mesothelioma in patients with neurofibromatosis type 2 (Baser *et al.*, 2002) or Li-Fraumeni syndrome (Heineman *et al.*, 1996) who are also exposed to asbestos. Several reports of familial cases of diffuse malignant mesothelioma are complicated by a common household exposure history (Weiner & Neragi-Miandoab, 2009). The strongest association between environmental exposure to erionite and genetic susceptibility to diffuse malignant mesothelioma has been provided by pedigree analysis of residents in the Cappadocia region of Turkey (Dogan *et al.*, 2006). However, there is skepticism about the accuracy of this analysis, and a recent review indicated that familial clusters can account for only 1.4% of cases of mesothelioma in Italy between 1978–2005 (Ascoli *et al.*, 2007; Ugolini *et al.*, 2008). One study has reported an association between genetic polymorphisms in the X-ray complementing group 1 gene (XRCC1) and the development of malignant mesothelioma in a population exposed to asbestos fibres (Dianzani *et al.*, 2006). More sensitive genome-wide association studies may uncover new markers for genetic susceptibility that predict increase risks of developing diffuse malignant mesothelioma following exposure to asbestos or erionite fibres.

4.5 Synthesis

The mechanistic basis for asbestos carcinogenicity is a complex interaction between crystalline mineral fibres and target cells *in vivo*. The most important physicochemical properties of asbestos fibres related to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Multiple direct and indirect mechanisms have been proposed based on numerous in-vitro cellular assays, and acute and subchronic animal bioassays. These complex mechanisms most likely interact at multiple stages during the development of lung cancer and diffuse malignant mesothelioma.

The following general mechanisms have been proposed for the carcinogenicity of asbestos fibres (Fig. 4.1; Fig. 4.2):

1. Direct interaction between asbestos fibres and target cells *in vitro*:
   - Asbestos and erionite fibres have been shown to generate free radicals that directly induce genotoxicity as assessed by DNA breaks and oxidized bases in DNA.
   - Asbestos fibres have also been shown to interfere with the mitotic apparatus by direct physical interaction resulting in aneuploidy and polyploidy.
2. Indirect mechanisms:
   - In laboratory animals, asbestos fibres have been shown to induce macrophage activation and persistent inflammation that generate reactive oxygen and nitrogen species contributing to tissue injury, genotoxicity, and epigenetic alterations. Persistent inflammation and chronic oxidative stress have been associated with the activation of intracellular signalling pathways, resistance to apoptosis, and stimulation of cell proliferation.

There are significant species differences in the responses of the respiratory tract to the inhalation of asbestos fibres. The biological mechanisms responsible for these species differences are unknown. Based on comparative animal experimental studies, there may be differences in deposition and clearance of fibres in the lungs, in severity of fibrosis, in kinetics of translocation of fibres to the pleura, and in levels or types of antioxidant defense mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite). Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.

There is *sufficient evidence* in experimental animals for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite).

All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are *carcinogenic to humans (Group 1)*.

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ERIONITE

Erionite was considered by previous IARC Working Groups in 1987 (IARC, 1987a, b). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Erionite (CAS Registry No.: 66733-21-9) is a naturally occurring fibrous mineral that belongs to a group of hydrated aluminosilicate minerals called zeolites (NTP, 2004). Its molecular formula is $(Na_2, K_2, Ca, Mg)_{4.5}Al_9Si_{27}O_{72}•27H_2O$) (IARC, 1987a).

1.2 Chemical and physical properties of the agent

Erionite is a natural fibrous zeolite, found in certain volcanic tuffs as an environmental contaminant. The basic structure of erionite series minerals is an aluminosilicate tetrahedron ($(Si,Al)O_4$) with oxygen atoms shared between two tetrahedra. Erionite is a 'chain silicate' composed of six tetrahedra on each edge of the unit (NTP, 2004). Although erionite has a similar morphology to that of amphibole asbestos (i.e. it has a chain-like structure), it has different chemical and physical properties (Metintas *et al.*, 1999). Erionite occurs as finely fibrous or wool-like white prismatic crystals, with a hexagonal physical structure, and an internal surface area approximately 20 times larger than that of crocidolite asbestos (IARC, 1987a; Metintas *et al.*, 1999; NTP, 2004). It has a density between 2.02–2.08, and absorbs up to 20% of its weight in water. Its gas absorption, ion exchange, and catalytic properties are highly selective and dependent upon the molecular or ionic size of the sorbed compounds as well as upon the cation content of erionite itself (IARC, 1987a). Erionite is not known to occur in other than fibrous form; however, the detailed morphology of erionite 'bundles' that are composed of many 'fibres' and 'fibrils' enhances its surface-area-to-volume ratio drastically (Dogan *et al.*, 2008).

1.3 Use of the agent

Natural zeolites have many commercial uses, most of which are based on the ability of these minerals to selectively absorb molecules from air or liquids. Erionite has been used as a noble-metal-doping catalyst in a hydrocarbon-cracking process, and studied for its use in agricultural applications (i.e. in fertilizers and odour control in livestock production) (IARC, 1987a; NTP, 2004). Erionite-rich blocks were historically quarried in the western United States of America for house-building materials, but this use was considered very minor, and not an

intentional use of erionite itself (IARC, 1987a). Natural erionite has not been mined or marketed for commercial purposes since the late 1980s, and has been replaced by synthetic non-fibrous zeolites (Dogan & Dogan, 2008).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Zeolite minerals are found as major constituents in numerous sedimentary volcanic tuffs, especially where these have been deposited and altered by the action of saline lake water (either by percolation or immersion). Erionite minerals occur as deposits of prismatic-to-acicular crystals in several different types of rock (e.g. rhyolite tuff), and in a wide range of geological settings. They rarely occur in pure form and are normally associated with other zeolite minerals (e.g. clinoptilolite, clinoptilolite-phillipsite). Erionite occurs as two major morphotypes: a short fibre form (named after the original Greek word for wool), and a long fibre form. When ground to powder, erionite fibres resemble amphibole asbestos fibres morphologically (IARC, 1987a; Dogan & Dogan, 2008).

Deposits of erionite have been recorded in Antarctica, Europe (Austria, the Czech Republic, France, Germany, Italy), Africa (Kenya, United Republic of Tanzania), Asia (the Republic of Korea, Japan), North America (USA, Canada, Mexico), as well as Georgia, Iceland, New Zealand, the Russian Federation, Scotland, and Turkey (Dogan & Dogan, 2008; Ilgren *et al.*, 2008).

The fibre size distribution of erionite from different deposits vary. Turkish erionite from Karain contains a higher proportion (32%) of longer fibres (> 4 μm) than erionite from Oregon, USA (11%) or New Zealand (8%). New Zealand and Oregon erionites contain 2–3% of thicker fibres (> 1 μm), whereas Karain erionite does not contain any such fibres (Ilgren *et al.*, 2008).

1.5 Human exposure

1.5.1 Exposure of the general population

Most of the non-occupational data on exposure to erionite refers to certain villages of the Cappadocia region, Turkey, where people are exposed to erionite throughout their lives. Erionite deposits in the USA are in remote desert regions where there is no stable population (Dogan *et al.*, 2008).

Dumortier *et al.* (2001) evaluated the fibre burden in bronchoalveolar lavage fluid (BALF) of 16 inhabitants of Tuzköy, an erionite-exposed village in the Cappadocia region of Turkey. All subjects were considered to have environmental exposure to erionite (because they were born in the village and had lived there for 10 years). Their fibre burden was compared to that of subjects with (n = 59) and without (n = 16) environmental exposure to tremolite asbestos. Ferruginous bodies (FBs) and fibres in the BALF were measured and analysed by phase–contrast light and transmission electron microscopy (TEM). FBs were detected by light microscopy in the BALF of 12 subjects; of these, seven had concentrations above 1 FB/mL. The geometric mean concentration of FBs was 1.33 FB/mL (95%CI: 0.35–3.04). In the TEM analysis, erionite accounted for 95.7% of the FBs. Erionite fibres were found in the BALF of all 16 subjects; nine subjects had concentrations higher than 300 f/mL. The mean concentration of erionite fibres in BALF was similar to that of tremolite fibres in subjects with environmental exposure to tremolite. Erionite accounted for 35.6% of fibres longer than 8 μm in BALF. Tremolite, in contrast, accounted for 14.0%. The asbestos fibre concentrations in erionite villagers was not different from that in subjects without environmental exposure to tremolite.

1.5.2 Occupational exposure

Historically, occupational exposure occurred from the mining and production of erionite. Erionite has also been reported to be a minor component in some commercial zeolites. Although erionite has not been mined for commercial purposes since the late 1980s, occupational exposure to erionite may still occur during the mining, production, and use of other zeolites (NTP, 2004).

2. Cancer in Humans

2.1 Pleural and peritoneal mesothelioma

At the end of the 1970s, a very high incidence of pleural mesothelioma was observed in one of the regions of Turkey, in three villages in Cappadocia where erionite was present (Sarihidir, Tuzköy, and Karain). During 1970–87, 108 cases of pleural mesothelioma were recorded in the small village of Karain (604 inhabitants in 1974) – equivalent to an annual incidence of more than 800 cases/100000, that is, about 1000 times the rate observed in the general population of industrialized countries. These cases were responsible for nearly half the deaths reported in this village. In Tuzköy, the annual incidence was estimated at 220 cases/100000. Overall, it was identical for men and women, the ratio of men/women was in the range of 1–2, according to series and village, and the mean age was roughly 50, with a range of 26–75 years (Bariş *et al.*, 1978; Simonato *et al.*, 1989). Artvinli & Bariş (1979) suggested that the presence of erionite in the soil, road dust and building stones of Tuzköy was probably the cause of the high incidence of mesothelioma, and other respiratory abnormalities. It was estimated that a cumulative yearly dose of 1 f/mL induces a pleural mesothelioma rate of 996/100000 persons–year in erionite villages (Simonato *et al.*, 1989).

Bariş & Grandjean (2006) extended the follow-up of the inhabitants of Sarihidir and Karain and another village without known exposure to erionite during 1979–2003. A total of 891 men and women, aged 20 years or older, were included, 230 of them from the village without exposure. During the 23-year follow-up, 372 deaths occurred; 119 of these from mesothelioma, which was the cause of 44.5% of all deaths in the exposed villages. Seventeen patients had peritoneal mesothelioma; the rest had pleural mesothelioma. Only two cases of mesothelioma, one of each type, occurred in the control village—both in women born elsewhere. When standardized to the world population, the pleural mesothelioma incidence was approximately 700 and 200 cases per 100000 people annually in the two exposed villages, respectively, and about 10 cases per 100000 people in the control village.

Other studies were published on a cohort of nearly 100 Karain natives who had emigrated to Sweden from the 1960s onwards. In the first of these, seven cases (four women, three men) of mesothelioma were observed (Özesmi *et al.*, 1990). In a follow-up to 1997 including 162 subjects (87 men and 75 women), Metintas *et al.* (1999) reported 14 (78%) deaths due to mesothelioma among the overall 18 deaths during 1965–97; this proportion was even higher than the proportion found in a Turkish study (49%) (Bariş *et al.*, 1996). The fact that the immigrant community was stable, and the diagnoses of mesothelioma were all histopathologically proven, gives strength to the findings. The average annual mesothelioma incidence rates in this cohort were about 135 times higher among the men and 1336 times higher among the women compared with the general population of Sweden during 1965–67. The total observed number of malignant pleural mesotheliomas (eight men and ten women) in this group resulted in a risk (mesothelioma standardized incidence ratio) in the men and women subjects of about 265 and 1992 times higher, respectively, than that of the

Swedish population (Metintas *et al.*, 1999). The men/women ratio of pleural mesothelioma in the cohort (0.8) was different from that of industrialized countries, where mesothelioma mostly occurs due to occupational exposure. Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-07-Table2.1.pdf presents the main results of pleural mesothelioma incidence and mortality in populations exposed to erionite in Cappadocia, Turkey.

Selçuk *et al.* (1992) studied 135 mesothelioma cases in Turkey from erionite (n = 58) and tremolite (n = 77) villages. The clinico-anatomical appearance of the malignancies was similar in subjects exposed to asbestos or erionite fibres, and pleural plaques were observed in all subjects. In both the erionite- and the asbestos-exposed groups, one quarter of the patients were less than 40 years of age, and the mean ages were not significantly different between the two groups (respectively, 46.4 and 49.7 years); the ages of the patients were in the range of 27–67 years in the erionite group and 26–75 years in the asbestos group, suggesting that the latent period was not specific to the type of fibre that patients were exposed to. Men and women were approximately equal in number in the erionite group (men/women ratio: 31:27); and men were the predominant gender in the asbestos group (men/women ratio: 51:26). However, this may be explained in part by referral bias, as populations from the three erionite villages were known as a high-risk group, and the patients were referred as soon as a presumptive diagnosis was made; in contrast, there was no equivalent system of survey in the asbestos villages where patients were not actively surveyed, but were admitted after presentation.

Gulmez *et al.* (2004) retrospectively evaluated 67 patients with mesothelioma observed during 1990–2001 in central Anatolia, Turkey. In 51 patients (76.1%), the mesothelioma was confined to the pleura, in 14 patients it was exclusively peritoneal, and in two patients, it involved both areas. Of the 67 cases, 35 (52.2%) were women; the mean age for all cases was 57.6 years. Environmental exposure to erionite and asbestos was found in 50.7% and 25.4% of the cases, respectively.

Some of the studies of erionite-induced mesothelioma in Turkey could not rely on full diagnosis assessment. X-rays and biopsy histology were available for many cases, but not for all. However, some studies were able to perform full histopathological examinations, such as the Selçuk *et al.* (1992) study, or the Swedish study of Karain emigrants (Özesmi *et al.*, 1990; Metintas *et al.*, 1999), and found associations of the same order of magnitude between erionite exposure and the risk of mesothelioma, giving strong confidence in the Turkish findings.

Some reports suggested that the simian virus 40 (SV40) could act as a co-carcinogen to induce mesothelioma (Carbone *et al.*, 2002). This is a controversial issue; however, this hypothesis can be excluded regarding erionite because SV40 DNA was never found in the specimen of Turkish patients (Emri *et al.*, 2000; Carbone *et al.*, 2007). Based on the fact that not all exposed villagers died from mesothelioma and that some families in erionite villages seemed to be at particularly high risk, the cause of the high incidence of mesothelioma was hypothetically attributed to the interaction of erionite exposure and genetic factors (Carbone *et al.*, 2007). Although it is not possible to exclude some genetic susceptibility, this hypothesis remains largely speculative and is not substantiated by sound data, because all relatives shared the same exposure to erionite since birth, except for some women who came from other villages, and because some mesotheliomas occurred in patients whose parents died from other causes, and vice versa (Bariş & Grandjean, 2006).

2.2 Other cancers

Bariş *et al.* (1996) also studied the cancer-specific mortality in the three Turkish erionite villages of Karain, Tuzköy, and Sarihidir. During 1970–94, 305 deaths were reported in Karain; of these, 177 (58%) were cancers, and included 150 cases (49.2%) of malignant pleural mesothelioma, seven cases (2.3%) of malignant peritoneal mesothelioma, and six (1%) of gastroesophageal carcinoma; four deaths (1.3%) from cancer of the lung included two non-smoking women; there were also three cases (1%) of leukaemia, and six of other malignancies (1.9%). During 1980–94, 519 deaths were reported in Tuzköy and Sarihidir (432 and 87, respectively); of these, 257 were cancers, and included 120 cases of malignant pleural mesothelioma, and 64 cases of malignant peritoneal mesothelioma; 30 patients had "intra-abdominal carcinoma" (according to the authors, some of them might have been peritoneal mesothelioma or ovarian carcinoma), and 14 patients had cancer of the lung (four of whom were non-smoking women); there were five cases of gastroesophageal cancer, five deaths due to leukaemia, and 16 cases of various malignancies including ovarian cancer, mesenchymal tumours, and leiomyosarcoma of the colon. These mortality figures lend some support to the hypothesis that erionite fibres also cause cancer other than mesothelioma and cancer of the lung; however, no statistical comparisons and no mineralogical analyses of the tissues were performed to demonstrate this relationship. Another difficulty is the uncertain validity of diagnoses. Bariş & Grandjean (2006) also looked at other cancers in their follow-up of the inhabitants of Sarihidir and Karain, but the small number of these cancers (n = 32, accounting for 9% of the total deaths) precluded a detailed analysis.

2.3 Synthesis

Studies of villages in Turkey where inhabitants were exposed from environmental sources from birth as well as the follow-up of a cohort of emigrants from one of the exposed villages in Sweden showed an extremely high incidence of pleural and peritoneal mesothelioma that can be causally associated with erionite exposure. The potency of erionite to induce mesothelioma seems much higher than for any type of asbestos.

3. Cancer in Experimental Animals

See Section 3 of the *Monograph* on Asbestos in this volume.

4. Other Relevant Data

See Section 4 of the *Monograph* on Asbestos in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of erionite. Erionite causes mesothelioma.

There is *sufficient evidence* in experimental animals for the carcinogenicity of erionite.

Erionite is *carcinogenic to humans (Group 1).*

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LEATHER DUST

Leather dust was considered by previous IARC Working Groups in 1980 and 1987 (IARC, 1981, 1987). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Leather is the product obtained by tanning skins and hides by any one of several methods. By convention, the term 'hide' generally refers to the skin-covering of larger animals (cows, steers, horses, buffaloes, etc.), and the term 'skins', to those of smaller animals (calves, sheep, goats, pigs, etc.). Although the physical properties of these different skins vary, their basic chemical, physical, and histological characteristics are similar (IARC, 1981).

1.2 Chemical and physical properties of the agent

The skin is mainly composed of proteins, although it also contains lipids, carbohydrates, inorganic salts, and water. From the point of view of leather manufacture, the proteins of the skin are the most important components. These proteins include collagen (constitutes the bulk of the fibrous portion), and reticulin (similar to collagen, but differing in its ability to combine readily with silver salts). Elastin, also a fibrous protein, is present in very small quantities, mainly in the grain area, and to a small extent in the blood vessels. Most of the non-collagenous proteins are removed during pre-tanning operations, which are effectively a means of preparing a matrix of relatively pure collagen fibres that will subsequently be stabilized by tanning (IARC, 1981).

Tanning is any process that renders animal hides or skins imputrescible without impairing their flexibility after drying. The most commonly used tanning agents have been vegetable tannins, and basic chromium (III) sulfate.

The vegetable tannins fall into two broad chemicals groups: hydrolysable tannins and condensed tannins. Condensed tannins are more complex chemical structures, and are more likely to be found in the bark or wood of a tree, whereas the hydrolysable tannins predominate in the leaves and fruits. Hydrolysable tannins are mainly glucosides (i.e. glucose esterified with polyhydroxyl phenyl carboxylic acids, such as gallic and ellagic acids) that readily ferment to release the free acid used in primitive tanning processes to control acidity. The chemistry of condensed tannins is complex, and they have been identified as oligomers containing 4–10 flavonoid units, each containing 4–6 hydroxyl groups. Molecular weights in non-aqueous solvents range from 1000–3000, although measurements in aqueous

Table 1.1 Leather uses in relation to type of hide or skin

Skin origin	Use
Cow and steer	Shoe and boot uppers, soles, insoles, linings; patent leather; clothing; work gloves; waist belts; luggage and cases; upholstery; transmission belting; sports goods; packings
Calf	Shoe uppers; slippers; handbags; wallets; hat sweatbands; bookbindings
Sheep and lamb	Grain and suede clothing; shoe linings; slippers; dress and work gloves; hat sweatbands; bookbindings; novelties
Goat and kid	Shoe uppers and linings; dress gloves; clothing; handbags
Pig	Shoe suede uppers; dress and work gloves; wallets; fancy leather goods
Deer	Dress gloves; moccasins; clothing
Horse	Shoe uppers; straps; sports goods
Reptile	Shoe uppers; handbags; fancy leather goods

Compiled by the Working Group

solution suggest aggregation or association to give an effective molecular weight of approximately 10000 (IARC, 1981).

In chrome tanning, the trivalent chromium ions form polynuclear complexes involving, typically, four chromium atoms. Ring structures containing coordinated sulfate and hydroxyl ligands are formed, giving an effective ionic weight of approximately 800. When skins are immersed in a solution of basic chromium (III) sulfate, carboxyl side chains on the collagen enter the coordination sphere of the chromium to form an insoluble complex. This reaction, which invariably involves cross-linking, is the basis of chrome tanning (IARC, 1981).

The composition of leather used in the leather-product industries varies. For example, leather used in shoe manufacture may come from the corium part of hide skin processed during tanning. The composition of crust leather varies depending on the tanning processes (Buljan *et al.*, 2000). The reported chromium (III) levels in dust from chrome-tanned leathers have varied from 0.1% to 4.5% by weight (IARC, 1981). Leather may also contain trace amounts of chromium (VI) formed by oxidation of trivalent chromium during the tanning process. For example, in a Danish study of 43 leather products, 35% ($n = 15$) contained chromium (VI) at levels above the detection limit of 3 mg/kg (Hansen *et al.*, 2002).

1.3 Use of the agent

The hides or skins from different animals possess unique physical properties that are inherent to the particular animal or breed of animal, due largely to differences in climate, type of feed, etc., to which the animal is exposed. They are thus used for different specific purposes (Table 1.1). For more detailed descriptions, refer to the previous *IARC Monograph* (IARC, 1981).

1.4 Occupational exposure

For detailed descriptions of historical exposures to leather dust and other agents in the workplace, refer to the previous *IARC Monograph* (IARC, 1981).

1.4.1 Extent of occupational exposure

Leather and leather-product industries have moved gradually from the industrialized countries to the developing world. For example, shoe manufacture in the United States of America decreased by more than 90% during 1965–2002, and the largest footwear exporter to the USA was the People's Republic of China (Markkanen & Levenstein, 2004). China produced 40% of all prepared shoes in the world at the end of the last century (Chen & Chan, 1999), and the

number of employees in shoe manufacture in China was estimated to be about 2 million (Wang *et al.*, 2006). It was reported that Asian countries supply over 80% of the footwear traded in the world market, and the largest production comes from China followed by India, Indonesia, Viet Nam, Thailand, and Pakistan (Vachayil, 2007). In several developing countries, large and medium-sized manufacturers and retailers are known to use subcontracting practices, informal employment, and so-called home-based shoe-making. There are no reliable estimates on the informal workforce, but it is assumed to be even higher than in the formal sector (Markkanen & Levenstein, 2004). According to statistics from the International Labor Organization, other major countries producing leather products were Mexico (n = 302000 employees), Brazil (n = 305000), Indonesia (n = 279000), the Russian Federation (n = 190000), and Italy (n = 168000) (ILO, 2004).

Although several million people are working in the leather and leather-product industries, only a fraction are exposed to leather dust and other air contaminants in the workplace. No worldwide estimates of the numbers of workers exposed were available to the Working Group.

1.4.2 Levels of occupational exposure

Leather dust concentrations in selected studies published since the previous *IARC Monograph* (IARC, 1981) are presented below.

(a) Footwear industry

In a Russian mortality study of 5185 shoe-manufacturing workers employed during 1940–76, Zaridze *et al.* (2001) reported leather dust concentrations in the range of 6.5–12 mg/m^3 in the following production departments: cutting, fitting, lasting and making, and finishing. In this factory, leather dust was present as a co-exposure with solvents and chloroprene.

Shoe repairers are exposed to the dusts generated during scouring. In a Finnish study of shoe repairers from 11 shops, the time-weighted average concentrations of dust were in the range of 0.07–1.0 mg/m^3 in the vicinity of the roughing, scoring, and finishing machines. The dust concentration depended on the age and type of the machine, and the performance of its local exhaust. Electron-microscopic studies showed that the dust samples collected during the machining of shoes contained leather, polymers, and finishing materials. Several degradation products of polymers were present. Dust was formed mainly during the machining of shoes. Dust samples contained also low concentrations of insoluble chromium (0.10–0.32 μg/m^3), and hexavalent chromium (0.01–0.08 μg/m^3) (Uuklainen *et al.*, 2002).

In a Polish study, dust concentrations were higher in shoe-repair shops than in shoe manufacture. In the repair shops, the recorded concentration of inhaled dust fraction was in the range of 0.5 mg/m^3 (glueing of shoes and soles, zipper exchange, and heel abrasion) to 0.9 mg/m^3 (sewing of uppers and scouring of heels), with high short-term (> 1 minute) fluctuations in the range of 0.1–14.6 mg/m^3. In the shoe factories, the mean concentration of inhalable particles (sample duration > 8 hours) was in the range of 0.12–0.91 mg/m^3, but there were high short-term (> 1 minute) fluctuations in the range of 0.62–6.4 mg/m^3 (Stroszejn-Mrowca & Szadkowska-Stańczyk, 2003).

(b) Leather-tanning and -processing industry

Dust is produced during several processes in tanning operations: chemical dust can be produced during the loading of hide-tanning drums; and leather dust impregnated with chemicals is produced during some mechanical operations, including buffing (IARC, 1981). Total dust levels (personal and static) measured in three countries were presented in Table 2 of the previous *IARC Monograph* (IARC, 1981).

Personal levels ranged from a low of 0.1 mg/m^3 in buffing to a high of 21 mg/m^3 in semi-automatic staking (IARC, 1981).

1.4.3 Particle size distribution

Leather dusts can contain both fibres and grains; the fibres can vary from 30–1200 μm in length and from 10–30 μm in diameter. Grains are usually < 10 μm in diameter. In several surveys in Italy, more than 50% of the total dust in tanneries were reported with having a particle diameter of < 5 μm (IARC, 1981).

Particle sizes have been measured in the dust generated at various workstations in the shoe trade in Poland. The median particle diameter was about 10 μm, and the proportion of extrathoracic particles which would lodge in the nasal fossae was 35–52%, depending on the occupation (Stroszejn-Mrowca & Szadkowska-Stańczyk, 2003).

1.4.4 Exposure to other agents

(a) Footwear industry

Appendices 5 and 6 of the previous *IARC Monograph* list the various chemicals which may occur in the footwear industry. Most are different solvents used in adhesives, lacquers or cleaning agents. They include petroleum hydrocarbons, chlorinated hydrocarbons, ketones, esters, and alcohols (IARC, 1981). Benzene was previously widely used as a solvent in the shoe industry, and exposure levels during that period may have been high. For example, in Italy, the estimated concentrations of benzene in one shoe factory during 1939–65 were in the range of 0–92 ppm (300 mg/m^3). The highest exposures occurred in 1954–60, and benzene was banned by legislation in Italy in 1965 (Seniori Costantini *et al.*, 2003).

Wang *et al.* (2006) reviewed 182 articles on benzene exposure in the shoemaking industry in China during 1978–2004. In 1979–2001, 65% of the measurements exceeded the national occupational exposure limit (OEL) of 40 mg/m^3 (13 ppm), and 20% of these exceeded 500 mg/m^3 (154 ppm). Benzene levels above 1000 mg/m^3 (308 ppm) were not uncommon, and some were in excess of 4500 mg/m^3 (1385 ppm). It was also reported that, in some cases, pure benzene was used during the 1980s. The national OEL was lowered to 6 mg/m^3 (2 ppm) in 2002, but only 24% of the reported measurements in 2002–04 were below the OEL. The average benzene levels in 2002–04 were 25.1 mg/m^3 (8 ppm) in fitting uppers with soles, and 73.6 mg/m^3 (23 ppm) in the making of soles. The tasks where exposure occurred most often were fitting uppers with soles, soles-making, uppers-embedding, and uppers-making. Benzene-based adhesives are now banned in China and the national standard for benzene in adhesives is regulated to be less than 0.5% (Wang *et al.*, 2006).

At a large shoe factory in Tianjin, China, as part of a cross-sectional study, Vermeulen *et al.* (2006) collected dermal, inhalation, and urine samples (n = 113) from 70 subjects performing representative tasks and operations at the plant. Mean airborne concentrations of benzene and toluene were 1.52 (standard deviation (SD) 2.82) and 7.49 (SD 11.60) ppm, respectively.

Historically, many toluene-based adhesives manufactured in China contained about 10–30% of benzene as impurity (Chen & Chan, 1999). Exposure to other solvents varies widely, but the levels in some factories may be high. For example, in Viet Nam the national OEL of toluene 100 mg/m^3 (26 ppm) was exceeded by six times or more in different sections of a shoe-manufacturing plant in 1996. The concentration of acetone was 6–18 times the Vietnamese OEL 200 mg/m^3 (84 ppm) (Chen & Chan, 1999).

Leather dust may also contain agents originating from the processing of leather in tanneries. Levels of chromium (VI) compounds in leather dust are usually very low (see Section 1.4.2a). Leather dust may also contain dyes. Dyes which have been used in the boot and shoe

industry include seven dyes classified by IARC in Group 2B (*possibly carcinogenic to humans*): CI Acid Red 114 (CAS, 6459-94-5), auramine (CAS, 492-80-8), benzyl violet 4B (CAS, 1694-09-3), Trypan blue (CAS, 72-57-1), Ponceau MX (CAS, 3761-53-3), Ponceau 3R (CAS, 3564-09-8), and Rosaline (CAS, 632-99-5) in Magenta (IARC, 1981).

Other agents that may or may not have occurred in the footwear industry include salts of chlorophenols (preservative of leather), acrylic resins, isocyanates (reactive primers, two-part adhesives), polyurethanes and other polymers (artificial leather), chloroprene (component of polychloroprene latex), and wood dust (making of wooden shoes and models) (IARC, 1981).

(b) Leather-tanning and -processing industry

Appendices 5 and 6 of Volume 25 list chemicals that may occur in leather tanning (IARC, 1981).

Exposure to chromium (III) salts or vegetable tannins may occur during the weighing and introduction of chromium salts into rotating drums. Also, small amounts of chromium (VI) may be present. Sodium chlorophenates may be used to prevent the deterioration of leather during tanning, and to protect it from mould. Other possible exposures in the tanyard are sulfuric acid and hydrogen sulfide. If dimethylamine is used in the tanning process, *N*-nitrosodimethylamine may be produced (IARC, 1981).

The use of benzidine-based dyes has been reported in the retanning, colouring, and fat-liquoring departments of the leather-tanning and –processing industry. A wide array of chemical solvents (e.g. tetrachloroethylene, toluene, xylene, methyl ethyl ketone and isopropanol), pigments, and waxes may be used in the finishing departments. Exposure to formaldehyde may also occur (IARC, 1981).

(c) Other leather-product industries

Exposures in industries producing leather bags, wallets, suitcases, leather-wearing apparel, harnesses, leather furniture and other miscellaneous leather goods are similar to those that occur in the footwear industry (see Section 1.4.2a).

2. Cancer in Humans

The boot and shoe industry was first reviewed in the previous *IARC Monograph* IARC (1981). The then Working Group reviewed the results of case series on cancer of the nasal cavity and paranasal sinuses (referred below as sinonasal cancer), several of which compared the history of exposure among adenocarcinoma cases to other cancer controls. The then *Monograph* Working Group also reviewed the results of case series and case reports of leukaemia, as well as other studies focused on bladder, lymphatic and haematopoietic, oral/pharyngeal, lung, and stomach cancer. The Working Group concluded that "Employment in the boot and shoe industry is causally associated with the development of nasal adenocarcinomas" and that "It is most likely that exposure to leather dust plays a role in the association." The Working Group also concluded that an increased risk for other histological types of nasal cancer "may exist." They also observed that "The occurrence of leukaemia and aplastic anaemia among shoe workers exposed to benzene is well documented." They noted that excesses of bladder cancer were associated with the leather industry, but it was not clear if these could be attributed to shoe workers. They also reported that hypothesis-generating studies had observed excesses associated with cancer of the lung, oral cavity, pharynx, and stomach.

The boot and shoe industry was re-reviewed as part of the previous *IARC Monograph* Supplement 7 (IARC, 1987). In the period

following the publication of Volume 25 several new studies had been published. The Working Group for supplement 7 had access to a new retrospective cohort study, three new proportionate mortality studies, as well as new case–control studies of sinonasal cancer and other cancer sites. The conclusions of the Working Group for Supplement 7 were concordant with those of Volume 25. They also concluded that nasal adenocarcinoma was associated with the boot and shoe industry, and that the highest risk was among those with high exposures to leather dust. They also noted that there was evidence for other types of nasal cancer, and that there was further evidence of an increased risk of leukaemia associated with exposure to benzene in the industry. Mixed evidence that may indicate an excess risk of bladder cancer among shoe workers was also noted. Some associations with lung, oral, pharynx, and stomach cancer as well as kidney cancer and mesothelioma were also observed.

In this *Monograph*, studies published in the time following Supplement 7, as well as others that were not previously considered, are reviewed. Of special note are the retrospective cohort studies. The previously reviewed retrospective cohort study of workers in the boot and shoe industry in three English towns (Pippard & Acheson, 1985) has been updated and the end of follow-up extended to 1991, and the cohort study of Florence shoe workers exposed to benzene (Paci *et al.*, 1989) has also been updated and the follow-up extended to 1991 for a pooled analysis (Fu *et al.*, 1996). A US study of shoe workers focused on exposure to solvents, mostly toluene (Walker *et al.*, 1993), has also been updated (Lehman & Hein, 2006). A Russian study of shoe manufacturing workers focused on exposure to chloroprene has also been published (Bulbulyan *et al.*, 1998). The results of registry-based studies are presented in Table 2.1. Descriptive studies with information based only on death certificates are not included. The methods and results of relevant cohort and related studies are summarized in Table 2.2. Only the most recent results are presented in cases where the cohorts were updated. Also included in Table 2.2 are the methods and results of the previously reported proportionate mortality studies.

The results of relevant case–control studies of sinonasal cancer, including those previously reviewed, are summarized in Table 2.3. Studies of other respiratory cancers are summarized in Table 2.4. Case–control studies of bladder cancer are summarized in Table 2.5. Case–control studies of other cancer sites are summarized in Table 2.6. For case–control studies, only those that assessed the association with boot/shoe workers, the broader category of leather products, or with leather dust are included. Those that explicitly included tannery workers, which have a very different set of exposures, were excluded.

2.1 Sinonasal cancer

An unusual high prevalence of sinonasal cancer among boot and shoe or other leather workers observed in case series from the Northamptonshire region of England first cast suspicion on a possible association between the malignancy and the occupation (Acheson *et al.*, 1970a, b; Acheson, 1976). In the period following the previous *IARC Monograph* Supplement 7, case series continued to report cases of sinonasal cancer among workers that had been employed as shoe workers or exposed to leather dust. For example, Barbieri *et al.* (2005) reported that seven of 100 epithelial sinonasal cancer cases in the Province of Brescia, Italy, were exposed to leather dust with an average latency of 44 years. A large French adenocarcinoma case series reported that 11 of 418 cases had been exposed to leather dust, whereas 353 had been exposed to wood dust (Choussy *et al.*, 2008). [The Working Group noted that even though leather workers are the second most frequently reported group in these sinonasal cancer case series, it is difficult to interpret these results without knowing

Table 2.1 Descriptive and census-based studies

Reference, location, name of study	Population description	Exposure assessment	Organ site (ICD code)	Exposure and histology	No. of cases/ deaths	RR* (95%CI) *(unless indicated otherwise)	Adjustment for potential confounders	Comments
Acheson *et al.* (1970a, b) Incidence study of nasal cancer in Northamptonshire United Kingdom	Comparison of the estimated rate among boot and shoe trade workers (1953–67) to expected numbers based on rates in the Southern Register Areas of England	Occupational history from medical records and mailed survey or interview	Sinonasal cancer, histologically confirmed carcinomas	Boot & shoe workers All types Adenocarcinomas Squamous carcinomas	 17 7 7	 8 [NR] 35 [NR] 4 [NR]	Age	
Acheson *et al.* (1981) Incidence study of nasal cancer in England and Wales United Kingdom	1602 cases diagnosed 1963–67 from The Office of Population Censuses and Surveys	Cases were categorized by occupation	Nasal cancer (160, 160.2–160.9)	All leather workers Shoe makers & repairers Cutters, lasters & sewers	26 – –	4.4[a] 7.1[a] 4.3[a]	SIR, adjusted for snuff and tobacco	[a]indicates significance at the 0.01 level
Acheson *et al.* (1982) Incidence study of nasal cancer in Northamptonshire United Kingdom	Comparison of the estimated rate among boot and shoe trade workers (1953–67) to expected numbers based on rates in Northamptonshire	Occupational history from medical records & mailed survey or interview	Sinonasal cancer	Male boot & shoe workers All types Adenocarcinomas Squamous carcinomas Preparation/ finishing	 27 11 9 21	 4.8 (3.5–7.9) 7.8 (3.7–14.3) 3.1 (1.4–5.9) 4.5 (2.8–6.8)	SIR, adjusted for age	
Olsen (1988) Pension fund cancer incidence linkage Denmark	382 Cases from the Danish Cancer Registry diagnosed 1970–84. Registry records linked with the Danish supplementary Pension fund	Longest held occupation from Pension Fund	Sinonasal cancer (160.0, 160.2–160.9)	Manufacture of leather products and footwear (except wooden shoes) Men Women	 3 1	 12.3 (3.1–33.4) 0.3 expected	SPIR	SPIR for women not provided

Table 2.1 (continued)

Reference, location, name of study	Population description	Exposure assessment	Organ site (ICD code)	Exposure and histology	No. of cases/ deaths	RR* (95%CI) *(unless indicated otherwise)	Adjustment for potential confounders	Comments
Andersen *et al.* (1999) Census cancer incidence linkage Nordic countries	Linkage of 1970 Census with incident cancer cases diagnosed in Denmark (1971–87), Finland (1971–90), Norway (1971–91) and Sweden (1971–89)	Leather and shoe workers	All cancers (140–204)	Men employed in the category of shoe and leather workers in the 1970 census	1436	1.1 (1.0–1.1)	SIR, adjusted for age and calendar period	
			Stomach (151)		92	1.0 (0.8–1.3)		
			Colon (153)		107	1.1 (0.9–1.4)		
			Rectum (154)		80	1.1 (0.9–1.4)		
			Nose (160)		11	2.9 (1.5–5.3)		
			Larynx (161)		25	1.1 (0.7–1.6)		
			Lung (162)		264	1.1 (0.9–1.2)		
			Kidney (180.0)		41	0.9 (0.6–1.2)		
			Bladder (181)		114	1.1 (0.9–1.3)		
			Acute leukaemia (204.3)		12	0.9 (0.5–1.6)		
			Other leukaemia (204.0–2, 4)		22	1.0 (0.6–1.5)		
Vasama-Neuvonen et. al. (1999) Census cancer incidence linkage Finland	892591 occupationally active Finnish women at 1970 Census linked with the Finnish Cancer Registry for incidence of ovarian cancer cases during 1971–95	Occupations with proportion exposed ≥ 20% exposure to leather dust using FINJEM	Ovary (183)	No exposure to leather dust		1.0 (ref)	SIR stratified for birth cohort, follow-up period and social status; adjusted for mean number of children, mean age at first birth and turnover rate	Partial overlap with Andersen *et al.* (1999)
				Low (> 0.009 mg/ m^3)		1.3 (1.0–1.8)		
				Medium/high		no data		
				Occupation:				
				Cutter for footwear	6	2.5 (0.9–5.4)		
				Pattern maker; cutter	27	1.7 (1.1–2.5)		
				Tanner, fellmonger, pelt dresser	3	0.8 (0.2–2.3)		
				Leather sewer	4	0.6 (0.2–1.5)		

Table 2.1 (continued)

Reference, location, name of study	Population description	Exposure assessment	Organ site (ICD code)	Exposure and histology	No. of cases/ deaths	RR* (95%CI) *(unless indicated otherwise)	Adjustment for potential confounders	Comments
Tarvainen *et al.* (2008) Census cancer incidence linkage Finland	All Finns born during 1906–45 (725868 men, 825528 women). Census data linked with the Finnish Cancer Registry 1971–95	Exposure to leather dust using FINJEM	Mouth and pharynx (exluding the nasopharynx) (140–149)	Shoe makers/ cobblers	2	17.4 (2.1–62.9)	SIR, adjusted for age, calendar period and socioeconomic status. Lag time 10 yr	Partial overlap with Andersen *et al.* (1999)
				Leather dust:				
				Low (< 5 mg/ m^3–yr)	5	0.9 (0.3–2.0)		
				Medium (5–19 mg/m^3–yr)	3	1.8 (0.4–5.1)		
				High (20+ mg/ m^3–yr)	0	0.0 (0.0–15.6)		

CI, confidence interval; FINJEM, Finnish job exposure matrix; NR, not reported; RR, relative risk; SIR, standardized incidence ratio; SPIR, standardized proportionate incidence ratio; yr, year or years

Table 2.2 Cohort studies of boot and shoe workers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Decouflé & Walrath (1983) USA	Analysis of 3754 deaths (2144 men, 1610 women) among shoe-manufacturing workers identified using union records. Non-whites and persons of unknown sex, race or age were excluded. Deaths were listed from 1966–77 inclusive as obituaries in union newsletters	None	All cancers (140–209)	Men	464	1.10[a]	PMRs calculated from observed and expected deaths adjusted for age and calendar period	[a] indicates statistical significance at the 0.05 level. No sinonasal cancers observed vs 2.2 expected
				Women	430	1.12[a]		
			Oral & pharynx (140–149)	Men (women: $n = 0$)	17	[1.35]		
			Stomach (151)	Men	25	[1.15]		
				Women	19	[1.43]		
			Rectum (154)	Men	22	[1.57[a]]		
				Women	19	[1.81[a]]		
			Liver/gallbladder (155–6)	Men	14	[1.82[a]]		
				Women	17	[2.02[a]]		
			Larynx (161)	Men (women: $n = 1$)	3	[0.48]		
			Lung (162–163)	Men	155	[1.20[a]]		
				Women	35	[0.92]		
			Bladder (188)	Men	11	[0.72]		
				Women	7	[1.37]		
			Kidney (189)	Men	6	[0.61]		
				Women	6	[0.98]		
			Leukaemia (204–207)	Men	20	[1.20]		
				Women	16	[1.24]		
Garabrant & Wegman (1984) Massachusetts USA	Analysis of death certificates of 1962 shoe workers (1195 men, 767 women) who died in Brockton, Haverhill or Peabody (Massachusetts) during 1954–74 identified by indication of an occupation in leather or shoe manufacturing on death certificates	None	All cancers (140–209)	Men	217	1.08	PMRs calculated from observed and expected deaths adjusted for age and calendar period	No sinonasal cancers observed
				Women	131	0.95		
			Oral & pharynx (140–149)	Men (women: $n = 0$)	5	0.93		
			Digestive tract (150–159)	Men	84	1.4 (1.1–1.7)		
				Women	44	0.99		
			Stomach (151)	Men	17	1.49		
				Women	5	0.82		
			Larynx (161)	Men (women: $n = 0$)	3	1.16		
			Lung (162)	Men	55	1.04		
				Women	13	1.07		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Garabrant & Wegman (1984) (contd.)			Bladder (188)	Men	5	0.56		
				Women	7	2.5 (1.2–5.1)		
			Leukaemia (204)	Men	8	0.95		
				Women	2	0.52		
Walrath *et al.* (1987) New York State USA	Analysis of 4734 death (3512 men, 1222 women) certificates from employees of one shoe-manufacturing company identified using newspaper obituaries. Deaths occurred during 1960–79	None	All cancers (140–209)	Men	689	1.09[a]		[a] indicates statistical significance at the 0.05 level No sinonasal cancers observed vs 1.9 expected
				Women	274	1.08		
			Oral & pharynx (140–149)	Men (women: $n = 1$)	22	1.22		
			Larynx (161)	Men (women: $n = 0$)	7	0.78		
			Lung and pleura (162 163)	Men	163	0.93		
				Women	18	0.84		
			Stomach (151)	Men	71	1.83[a]		
				Women	14	1.28		
			Colon (153)	Men	100	1.53[a]		
				Women	49	1.41[a]		
			Rectum (154)	Men	33	1.42[a]		
				Women	16	1.97[a]		
			Bone (170)	Men (women: $n = 0$)	6	2.23[a]		
			Bladder (188)	Men (women: $n = 1$)	24	0.91		
			Kidney (189)	Men	16	1.16		
				Women	5	1.17		
			Multiple myeloma (203)	Men	10	1.93[a]		
				Women	8	3.46[a]		
			Leukaemia (204–207)	Men	22	0.86		
				Women	7	0.79		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Fu *et al.* (1996) United Kingdom and Italy	Pooled analysis of 2 updated shoe-manufacturing cohorts. 4215 English (follow-up 1950–91, Pippard & Acheson, 1985) and 2008 Italian (follow-up 1950–90, Paci *et al.*, 1989) shoe workers	Workers classified as exposed to leather dust or solvents based on work history (Italian) or 1939 Census (English)	All causes (001–999)	English cohort	3314	0.8 (0.8–0.8)	SMR, adjusted for sex, age, & calendar period using national rates	High exposure to benzene in the Italian cohort before 1963. Exposure to leather dust in the English cohort in the range of 0.5–7.5 mg/m³ in 1976
				Italian cohort	333	0.9 (0.8–1.0)		
			All cancers (140–208)	English cohort	646	0.8 (0.7–0.8)		
				Italian cohort	127	1.2 (1.0–1.4)		
			Stomach (151)	English cohort	77	0.7 (0.6–0.9)		
				Italian cohort	25	1.9 (1.2–2.8)		
			Colon (153)	English cohort	57	0.9 (0.7–1.2)		
				Italian cohort	10	1.7 (0.8–3.0)		
			Rectum (154)	English cohort	51	1.1 (0.8–1.4)		
				Italian cohort	5	1.4 (0.5–3.3)		
			Pancreas (157)	English cohort	25	0.7 (0.5–1.0)		
				Italian cohort	2	0.5 (0.1–2.0)		
			Nose (160)	English cohort	12	8.1 (4.2–14.1)		
				Probable leather dust	9	11.7 (5.3–22.2)		
				High leather dust	1	25.0 (0.6–139)		
				Probable solvent	2	3.9 (0.5–13.9)		
				High solvent	0	0		
				Italian cohort	1	13.0 (0.31–70.0)		
				Probably leather dust	0	0.0		
				High leather dust	0	0.0		
				Probable solvent	1	20 (0.5–99)		
				High solvent	1	20 (0.5–99)		
			Larynx (161)	English cohort	6	0.7 (0.2–1.4)		
				Italian cohort	2	0.7 (0.1–2.5)		
			Lung (162)	English cohort	186	0.6 (0.5–0.7)		
				Italian cohort	24	1.0 (0.7–1.5)		
			Bone (170)	English cohort	6	2.1 (0.8–4.5)		
				Italian cohort	0	0		
			Bladder (188)	English cohort	34	0.8 (0.6–1.2)		
				Italian cohort	3	0.9 (0.2–2.51)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Fu *et al.* (1996) (contd.)			Kidney (189)	English cohort	8	0.7 (0.3–1.4)		
				Probable leather dust	5	0.9 (0.3–2.0)		
				High leather dust	1	3.1 (0.1–17.4)		
				Probable solvent	1	0.3 (0.01–1.4)		
				High solvent	0	0		
				Italian cohort	3	2.2 (0.5–6.3)		
				Probable leather dust	0	0 (0–18.5)		
				High leather dust	0	0 (0–92.2)		
				Probable solvent	3	3.5 (0.7–10.3)		
				High solvent	3	4.0 (0.8–11.7)		
			Multiple myeloma (203)	English cohort	7	1.0 (0.4–2.1)		
				Probable solvent	3	1.2 (0.2–3.4)		
				High solvent	1	5.3 (0.1–29.3)		
				Italian cohort	3	3.7 (0.8–10.8)		
				Probable solvent	1	2.2 (0.5–12.1)		
				High solvent	1	2.4 (0.6–13.6)		
			Leukaemia (204–208)	English cohort	14	0.9 (0.5–1.4)		
				Probable solvent	4	0.7 (0.2–1.8)		
				High solvent	0	0 (0–7.9)		
				Italian cohort	7	2.4 (1.0–5.0)		
				Probable solvent	4	2.5 (0.7–6.4)		
				High solvent	4	2.8 (0.8–7.2)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Bulbulyan *et al.* (1998) Russian Federation	Retrospective study of 5815 Russian shoe-manufacturing workers (4569 women, 616 men) employed for 2 mo during 1940–76, followed from 1979 through 1993. Workers employed in auxiliary departments and management employees were excluded	Exposure categories based on chloroprene industrial hygiene data from 1970s Chloroprene exposure: High, 20 mg/m^3 (with co-exposures of benzene) Medium, 0.4–1 mg/m^3 (with co-exposures of formaldehyde, leather dust) No exposure (with co-exposure of leather dust)	All causes (001–999)	Full cohort	900	1.03 (0.97–1.1)	SMR, adjusted for age and sex using 1992 Moscow rates. RR in dose–response analysis adjusted for sex, age, gender and calendar period	Bladder cancer among men SMR, 2.1 (95%CI: 0.4–6.1) All 5 leukaemia cases in the high chloroprene exposure group employed before 1960 RR, 4.1 (95% CI: 1.1–17), co-exposure to benzene possible
				Any chloroprene	640	1.1 (1.0–1.3)		
				Medium chloroprene	446	1.1 (0.9–1.3)		
				High chloroprene	194	1.2 (1.0–1.5)		
			All cancers (140–208)	Full cohort	265	1.2 (1.1–1.4)		
				Any chloroprene	184	1.0 (0.8–1.3)		
				Medium chloroprene	128	1.0 (0.8–1.4)		
				High chloroprene	56	1.2 (0.9–1.7)		
			Stomach (151)	Full cohort	48	1.2 (0.9–1.6)		
				Any chloroprene	36	1.3 (0.7–2.6)		
				Medium chloroprene	26	1.3 (0.7–2.7)		
				High chloroprene	10	1.3 (0.3–3.1)		
			Colon (153)	Full cohort	21	1.1 (0.7–1.7)		
				Any chloroprene	16	1.4 (0.5–3.8)		
				Medium chloroprene	8	0.9 (0.3–2.8)		
				High chloroprene	8	2.6 (0.8–7.9)		
			Rectum (154)	Full cohort	14	1.1 (0.6–1.9)		
				Any chloroprene	8	0.7 (0.2–2.0)		
				Medium chloroprene	6	0.7 (0.2–2.3)		
				High chloroprene	2	0.5 (0.1–2.7)		
			Liver (155)	Full cohort	10	2.4 (1.1–4.3)		
				Any chloroprene	9	4.2 (0.5–33)		
				Medium chloroprene	6	3.8 (0.5–34)		
				High chloroprene	3	4.9 (0.5–47)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Bulbulyan *et al.* (1998) (contd.)			Lung (162)	Full cohort	31	1.4 (0.9–2.0)		
				Any chloroprene	23	0.9 (0.4–2.2)		
				Medium chloroprene	18	0.9 (0.4–2.1)		
				High chloroprene	5	1.1 (0.4–3.5)		
			Kidney (189)	Full cohort	10	1.8 (0.9–3.4)		
				Any chloroprene	9	3.8 (0.5–31)		
				Medium chloroprene	7	4.1 (0.5–34)		
				High chloroprene	2	3.3 (0.3–37)		
			Leukaemia (204–208)	Full cohort	13	1.9 (1.0–3.3)		
				Any chloroprene	9	1.1 (0.3–3.7)		
				Medium chloroprene	4	0.7 (0.2–2.7)		
				High chloroprene	5	2.2 (0.6–8.4)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Lehman & Hein (2006) USA	Update of Walker *et al.* (1993). An SMR analysis of 7828 shoe-manufacturing workers (2545 men, 5283 women) employed for 1 mo or more during 1940–79 at two Ohio manufacturing plants	Exposure data was based on toluene industrial hygiene data from 1970s. Toluene exposure by duration of employment for specific cancers (< 6 mo, 6 mo–1 yr, 2 yr– < 10 yr, > 10 yr)	All causes (0–999)	Men	1367	1.1 (1.0–1.1)	SMR, adjusted for age and calendar period	Results for sinonasal cancer not reported. Reported 'no evidence of any significant level of exposure to leather dust' Reported 'Benzene was not detected in these surveys and company management asserted that benzene had never been present in the solvents used at either of the plants.'
				Women	1768	1.0 (1.0–1.1)		
				Employment:				
				1 mo– < 6 mo	831	1.0 (1.0–1.1)		
				6 mo–2 yr	747	1.0 (1.0–1.1)		
				2 yr– < 10 yr	838	1.1 (1.0–1.2)		
				≥ 10 yr	719	1.0 (1.0–1.1)		
			All cancers (140–208)	Men	314	1.1 (1.0–1.2)		
				Women	482	1.0 (0.9–1.1)		
				Employment:				
				1 mo– < 6 mo	233	1.1 (1.0–1.3)		
				6 mo–2 yr	202	1.1 (0.9–1.2)		
				2 yr– < 10 yr	202	1.0 (0.9–1.2)		
				≥ 10 yr	159	0.9 (0.8–1.1)		
			Buccal cavity & pharynx (140–149)	Men	8	1.1 (0.5–2.2)		
				Women	1	0.2 (0.0–1.0)		
			Stomach (151)	Men	4	0.3 (0.1–0.8)		
				Women	6	0.5 (0.2–1.1)		
			Lung (162)	Men	138	1.4 (1.2–1.7)		
				Women	110	1.3 (1.0–1.5)		
				Employment:				
				1 mo– < 6 mo	75	1.5 (1.2–1.9)		
				6 mo–2 yr	74	1.6 (1.3–2.0)		
				2 yr– < 10 yr	52	1.1 (0.8–1.5)		
				≥ 10 yr	47	1.2 (0.9–1.5)		
			Bladder (188, 189.3–189.9)	Men	9	1.1 (0.5–2.1)		
				Women	6	1.0 (0.4–2.2		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Lehman & Hein (2006) (contd.)			Kidney (189.0–189.2)	Men	6	0.9 (0.3–1.9)		
				Women	8	1.1 (0.5–2.1)		
			Leukaemia (204–208)	Men	8	0.7 (0.3 –1.4)		
				Women	19	1.2 (0.7–1.9)		
				Employment:				
				1 mo– < 6 mo	8	1.1 (0.5–2.2)		
				6 mo–2 yr	4	0.6 (0.2–1.6)		
				2 yr– < 10 yr	9	1.3 (0.6–2.5)		
				≥ 10 yr	6	1.0 (0.4–2.2)		

CI, confidence interval; mo, month or months; PMR, proportional mortality ratio; RR, relative risk; SMR, standardized mortality ratio; vs, versus; yr, year or years

Table 2.3 Case–control studies on sinonasal cancer in shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Cecchi *et al.* (1980) Hospital-based Florence, Italy 1963–77	Nose and paranasal sinuses	66 cases (46 men, 20 women) diagnosed with adenocarcinoma in Florence, records from the Otorhinolaryngology clinic and the Radiology Insititute of the University of Florence	Controls were matched to cases by sex, age (± 5 yr), place of residence, smoking habits and year of hospital admission. Each case had 2 non-cancer controls admitted to the department of internal medicine in the hospital	Social worker interview to collect data on occupational history	Shoe makers		Adenocarcinomas 7/11 cases 0/22 controls ($P < 0.001$)	Matched on sex, age, place or residence (as surrogate for SES), smoking habits and year of admission	
Hardell *et al.* (1982) Sweden 1970–79	Nose (ICD 160)	44 cases, age 25–85 and residents of Southern Sweden reported to the Swedish Cancer Registry 1970–79	541 controls referents from another study with the same region, 1970–78	Work history from mailed questionnaire	Leather work		1 case (2.8%) vs 5 controls (0.9%)		Case was 1 of 3 adenocarcinomas
Brinton *et al.* (1984) Hospital-based N. Carolina & Virginia, USA 1970–80	Nasal cavity and sinuses (160.0, 160.2–160.5, 160.8–160.9)	193 incident cases from 4 hospitals	2 controls per case matched on age, sex, race, and region. 232 hospital & 140 death certificate controls (deceased cases had 1 living & 1 dead control)	Telephone interview with subject or next-of-kin	Leather or shoe industry Leather exposure		1.3 (0.1–9.4) 0.7 (0.2–2.0)	Adjusted for sex	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Merler *et al.* (1986) Vigevano, Italy 1968–82	Nasal epithelial tumours Nasal adenocarcinomas	21 cases (16 men, 5 women) from otolaryngology departments of three hospitals, the hospital cancer registry of the National Cancer Institute of Milan and city mortality records	2 controls per case were selected from the general population and matched by vital status, age, sex and residence	Interview to obtain occupational history. Estimated level of exposure based on specific tasks, workplaces, duration, technology and hygienic evaluation	Light/Uncertain Heavy Light/Uncertain Heavy	7 11 5 8	All epithelial tumours: 7.5 (1.8–31.7) 121 (17.3–844.3) Adenocarcinoma: 20.4 (2.7–152.0) 88.0 (12.1–642.0)	Matched on age, sex, and residence	Matched and unmatched analyses yielded similar results. Unmatched results presented
Bimbi *et al.* (1988) Hospital-based Milan, Italy 1982–85	Nasal cavity and paranasal sinus (160.0–160.9) (epithelial neoplasms)	53 (40 men, 13 women) cases admitted to the Head and Neck Oncology Department of the National Institute for Study and Treatment of Cancer in Milan	217 controls selected from patients admitted in the same yr with malignant tumour of the nasopharynx, thyroid or salivary glands	Occupational history was taken from hospital records	Leather workers (3 cases, 0 controls)		RR is reported as incalculable because 0 controls reported working in the leather industry		
Loi *et al.* (1989) Hospital-based Pisa, Italy 1972–83	Nasal cavity and paranasal sinus (160.0–160.9)	38 incident cases (all male) of nasal and paranasal sinus cancer admitted to Pisa University Hospital between October 1972 and October 1983	186 hospital controls (5:1 match) matched for sex, age (± 3 yr), province of usual residence, admission date (± 6 mo), excluding nasal tumours, respiratory tract malignancies and lymphomas	Mailed-out questionnaire on employment in leather-working industries & specific occupational risk factors	Leather exposure: All tumours		8.1 (2.0–33.5)	Matched on age, sex, and residence	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Shimizu *et al.* (1989) Hospital-based Japan 1983–85	Maxillary sinus (160.2), squamous cell carcinomas only	66 cases aged 42–77 yr (45 men, 21 women) October 1983 to October 1985 six university hospitals in six prefectures	132 controls were randomly selected from the same jurisdiction as the cases residence and matched for age (± 5 yr) and sex (2:1 match)	Self-administered questionnaires, occupational exposures and other risk factors	Leather workers		2.1 (0.1–38.3)	Matched on age and sex	
Bolm-Audorff *et al.* (1989, 1990) Hospital-based Hessia, Germany 1983–85	Nasal and paranasal sinus cancer (160)	62 cases identified through 85 otorhinolaryngogical and 8 pathology departments	Patients with non-occupational bone fractures matched on age, sex, and residence	In-person interviews	Leather dust exposure		2/62 cases and 0/62 controls	Matched on age, sex, and residence	
Comba *et al.* (1992a) Hospital-based Verona, Vicenza, Siena, Italy 1982–87	Nasal cavity and paranasal sinus (160) (epithelial neoplasms)	78 cases (55 men, 23 women) from the University of Verona Institute of Pathology and ENT Clinic, ENT departments at the hospitals of Vincenza, Bussolengo, and Legnago and Institute of Pathology at the University of Siena	254 controls (184 men, 70 women) admitted to the same hospitals (excluding chronic rhinosinusal disease and actute nasal bleeding) matched for admission date, hospital, sex, age (± 5 yr) & residence	Interviews and/or mailed questionnaires collected information on occupational history with specific questions for leather workers	Leather workers Shoe makers Associated with leatherwork: Adenocarcinoma Squamous cell carcinoma	5	6.8 (2.2–15) 8.3 (1.9–36) 14.1 (2.6–76) 1.6 (0.21–12)	Matched on age, sex, and residence. 90% confidence limits used	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Comba *et al.* (1992b) Hospital-based Brescia, Italy 1980–89	Nasal cavity and paranasal sinus (160) (epithelial neoplasms)	35 cases diagnosed and treated by the ENT department of the radiotherapy unit of the Brescia Hospital	102 controls from ENT department and radiotherapy unit files with neoplastic diseases of the head and neck and matched for age (± 5 yr) and sex	Telephone interview to collect detailed occupational history, specific items related to shoe-manufacturing industries	Leather workers (1 case)		9.0	Matched on age and sex	
Magnani *et al.* (1993) Hospital-based Biella, Italy 1976–88	Nasal cavity and paranasal sinus (160.0, 160.2–160.9) (epithelial or unspecified neoplasms)	33 cases identified by the Local Health Authorities of Biella and Cossato	131 controls (4:1 match) randomly chosen and matched on age and sex admitted same hospital, same year	Mailed questionnaire to patient and next-of-kin with work history	Shoe-manufacturing or other leather industries	3	3.5 (0.6–2.-0.3)	Matched on age and sex	
Luce *et al.* (1992, 1993) Population-based France 1986–88	Nasal cavity and paranasal sinus (160.0, 160.2–160.9)	207 (167 men, 40 women) cases of primary malignancies of the nasal cavity and paranasal sinuses diagnosed between January 1986 and February 1988 at 27 hospitals in France	409 controls were obtained from: 1) hospital cancer patients, frequency-matched for age and sex 2) controls selected from lists provided by cases matching for sex, age (± 10 yr), and residence	Physician interview to collect detailed occupational history	Shoe and leather workers: Ever employed < 15 yr > 15 yr 15 yr induction Leather dust: Medium-high level	3 3	Squamous cell carcinomas: 2.1 (0.5–8.3) 1.9 (0.2–18.3) 2.3 (0.4–12.3) 2.1 (0.5–8.3) 3.1 (0.8–12.4) Adenocarcinomas: 0 cases identified	Matched on age and sex	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Battista *et al.* (1995) Population-based Italy	Nasal cavity and paranasal sinus (160)	96 cases of malignant neoplasms of the nose and paranasal sinuses diagnosed during 1982–87 in the catchment areas of the hospitals of Verona, Vicenza and Siena	378 hospital controls matched for sex, age (± 5 yr), residence and time of admission; all diagnoses were accepted except chronic rhinosinusal disease, acute nasal bleeding	Interviews or mailed questionnaires to collect work history with specific questions in particular industries	Association with occupation: Leather workers Shoe makers	 2	 6.8 (1.9–25) 8.3 (1.9–36)	Matched on age, sex, and residence. 90% confidence limits used	
Teschke *et al.* (1997) Population-based Canada	Nasal cavity and paranasal sinus (160)	All incident cases with histologically confirmed primary malignant tumours age ≥ 19 yr, 1990–92	Controls were selected randomly from 5-yr age and sex strata of the provincial voters list; frequency-matched for age and sex	Occupational histories were obtained by interview	Shoe and leather workers		0/48 cases and 6/159 controls	Adjusted for age, sex, and smoking	
't Mannetje et al. (1999a) Pooled analysis Italy, France, Netherlands, Germany, Sweden	Nasal cavity and paranasal sinus (160) Adenocarcinomas and squamous cell carcinomas	555 cases (451 men, 104 women)	1705 controls (1464 men, 241 women) from the same studies. The control:case ratio ranged from 1 to 12.3, with an overall ratio of 3.1	Interviews were conducted to collect lifetime occupational histories. Exposures assessed with a job–exposure matrix	Exposure to leather dust: Women Men Adenocarcinomas Squamous cell carcinomas	 7 26 15 10	 2.7 (0.8–9.4) 1.9 (1.1–3.4) 3.0 (1.3–6.7) 1.5 (0.7–3.0)	Adjusted for age, study, sex (when applicable), smoking (when applicable)	The attributable risk for sinonasal cancer in relation to occupation was 33%. Data from Hardell *et al.* (1982), Hayes et al. (1986), Merler *et al.* (1986), Bolm-Audorff et al. (1989), Comba *et al.* (1992a, b), Luce *et al.* (1992), and Magnani *et al.* (1993)

CI, confidence interval; OR, odds ratio; RR, relative risk; SES, socioeconomic status; yr, year or years

Table 2.4 Case–control studies on respiratory cancer in shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders
Gustavsson *et al.* (1998) Community-based Sweden 1988–91	Oral cavity (143–145), pharynx (146–149), larynx (161), oesophagus (150)	545 incident cases (all male) of squamous cell carcinomas taken from the entire population of Swedish men aged 40–79 living in Stockholm or the southern region of Sweden	641 controls (all male) frequency-matched to cases for age and region	Interviewed by nurses on smoking history, use of oral snuff, alcohol habits and occupational history	Leather dust: All sites Oral cavity Pharynx Larynx Oesophagus	 16 3 5 5 3	 2.1 (0.9–4.9) 2.2 (0.5–8.7) 2.8 (0.8–10.2) 2.1 (0.7–6.6) 2.6 (0.6–10.7)	Matched on age and region. Adjusted for alcohol and smoking
Laforest *et al.* (2000) Population-based France 1989–91	Larynx (161) and hypopharynx (148) (squamous cell only)	497 incident (all male) histologically confirmed cases from 15 French hospitals	296 cancer controls from the same medical environment as cases were matched for age and recruited during 1987–91 in the same or nearby hospitals	Occupational physician interview to collect data on lifetime occupational history. Exposures assessed with a job–exposure matrix	Exposure to leather dust: Never exposed Ever exposed Never exposed Ever exposed	 288 8 198 3	Larynx 1.0 0.9 (0.6–1.3) Hypopharynx 1.0 0.8 (0.2–4.1)	Adjusted for age, smoking and alcohol consumption
Jöckel *et al.* (2000) Pooled analysis Germany 1988–93, 1990–96	Lung (162)	4184 (3498 men, 868 women) identified during 1988–93 in Bremen, Frankfurt, and during 1990–96 in North Rhine-Westphalia, Rhineland-Palatinate, East Bavaria, the Saarland, Thuringia, and Saxony	4253 (3541 men, 712 women) population controls matched for sex, age, and region of residence	Interviewed to collect information on job history and occupational exposure	Shoe workers: Men– Ever employed Exposed > 0–3 yr > 3–30 yr > 30 yr Women– Ever employed Exposed > 0–3 yr > 3–30 yr > 30 yr	 63 18 33 12 13 7 6 0	 1.6 (1.0–2.5) 0.7 (0.3–1.4) 2.5 (1.2–5.1) 2.8 (0.9–9.2) 2.7 (0.8–8.8) 3.6 (0.4–32.1) 3.0 (0.6–14.5) no data	Adjusted for smoking and asbestos exposure

Table 2.4 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders
Matos *et al.* (2000) Hospital-based Argentina 1994–96	Lung (162)	199 male patients residents in the city or in the province of Buenos Aires and admitted for treatment in any of four hospitals	393 controls; two male control subjects hospitalized for conditions unrelated to tobacco use during the same period and residents in the same area, matched by hospital and age (± 5 yr)	Occupational history obtained by interview; occupational exposure assessed by job–exposure matrix	Occupation: leather shoes & repair Industry: leather shoes & repair	8 12	1.5 (0.5–4.2) 2.2 (0.8–5.8)	Adjusted for age group, hospital, pack–year and industries with $P < 0.05$
Boffetta *et al.* (2003) Pooled analysis France Italy, Spain, Switzerland 1980–83	Larynx (161) and hypopharynx (148)	1010 male cases with histologically confirmed epidermoid carcinomas from Turin, Varese, Pamplona, Calvados, Zaragoza, and Geneva	2176 population-based controls from the same centres, chosen census lists, electoral roles, or population registries	Occupational histories collected by interview	Larynx/ hypopharynx Shoe makers/ repair Shoe finishers Larynx Only Shoe finishers 1–10 yr 11–20 yr 21+ yr	 15 7 3 4 0	 1.2 (0.6–2.6) 3.2 (0.8–13.9) 4.4 (1.0–18.8) 4.6 2.7 0.0	Adjusted for age, centre, alcohol, and smoking

CI, confidence interval; OR, odds ratio; yr, year or years

Table 2.5 Case–control studies on cancer of the bladder in shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Cole *et al.* (1972) Population-based Massachusetts, USA	Bladder and lower urinary tract	461 histologically confirmed cases of transitional or squamous cell carcinoma	485 controls selected from the same sex and age from residents lists for the area	Lifetime work history collected by interview	Men: leather products	79	2.0 (1.4–2.9)	Age and smoking	
					Finishing & associated	44	2.7 (1.6–4.5)		
					Contact with finished	13	1.7 (0.9–3.4)		
Silverman *et al.* (1983) Population-based Detroit, USA 1977–78	Bladder and lower urinary tract	303 male, histologically confirmed transitional or squamous cell carcinoma cases identified by 60/61 hospitals in the region	296 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases	Lifetime work history collected by interview	Leather & leather products manufacture & repair	4	0.5 (0.1–1.6)	Unadjusted	
					Shoe repairman and bootblack	3	0.7 (0.2–3.3)		
Schoenberg *et al.* (1984) Population-based New Jersey, USA 1978–79	Bladder (188)	658 male, histologically confirmed carcinoma cases	1258 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases	Lifetime work history collected by interview	Leather worker	19	1.8 (0.9–3.5)	Age and smoking	
					Leather products	6	1.2 (0.4–3.6)		
					Shoe repair/ bootblack	9	1.9 (0.7–5.1)		
					Leather materials	34	1.9 (1.1–3.2)		

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Marrett *et al.* (1986) Population-based 10 areas, USA 1978–79	Bladder	2982 histologically confirmed carcinoma cases	5782 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases	Lifetime work history collected by interview	Leather dust < 5 yr 5–14 yr 15+ yr	42 21 6 13	1.4 (0.9–2.1) 1.6 (0.9–2.8) 0.8 (0.3–1.9) 1.4 (0.7–3.0)	Unadjusted	
Silverman *et al.* (1989) Population-based 10 areas, USA 1977–78	Bladder	2100 histologically confirmed white male carcinoma cases. 75% of cases were interviewed.	3874 white male controls selected through random-digit dialling (84% interviewed) or random selection from Health Care Finance Administration lists (83% interviewed) selected to be similar in age to cases	Lifetime work history collected by interview	Leather-processing workers	13	1.2 (0.6–2.7)	Smoking	Further adjustment for age, area, education and other factors had no effect
Schumacher *et al.* (1989) Population-based Utah, USA 1977–83	Bladder (188)	417 (332 men and 85 women) cases identified by the Utah cancer registry	877 (685 men and 192 women) controls selected by random-digit dialling or randomly from Health Care Finance Administration lists, frequency-matched on sex and age	Lifetime occupational histories obtained by interview	Men: Ever Leather industry < 10 yr ≥ 10 yr > 45 yr before diagnosis Men: leather dust Women: leather dust	 2 1	1.4 (0.5–4.0) 1.4 (0.5–4.6) 1.2 (0.1–13.4) 3.0 (0.6–13.8) 0.8 (0.1–5.1) 2.3 (0.03–179)	Age, smoking, religion, education	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Siemiatycki *et al.* (1994) Population-based case-control study Montreal, Canada 1979–86	Bladder	484 cases among male residents of the Montreal area	1879 cancer cases from the same large study (all sites, excluding kidney) and 533 population controls from random-digit dialling	Extensive interview review by exposure assessment team	Leather workers: < 10 yr ≥ 10 yr Shoe makers: < 10 yr ≥ 10 yr Leather dust: Substantial Non-substantial	 12 14 5 1 8 5	 1.0 (0.5–1.9) 0.7 (0.4–1.3) 2.0 (0.7–5.6) 0.3 (0.0–2.0) 0.7 (0.3–1.5) 0.6 (0.2–1.5)	Age, ethnicity SES, smoking, and coffee consumption	
Teschke *et al.* (1997) Population-based Canada 1990–92	Bladder (188)	All incident cases (n = 105) with histologically confirmed primary malignant tumours age ≥ 19 yr	Controls (n = 139) selected randomly from 5-yr age and sex strata of provincial voters list; frequency-matched for age and sex	Occupational histories were obtained by interview	Shoe and leather workers	2	0.4 (0.1–2.6)	Age, sex, and smoking	
't Mannetje *et al.* (1999b) Re-analysis of 11 population-based studies Germany, France, Italy, Greece, Denmark, Spain, 1976–96	Bladder	700 incident female cases, age 30–79 yr	2425 population-based or hospital controls individually or frequency-matched on age group and geographic area	Lifetime occupational history	Shoe makers and leather goods makers	7	0.4 (0.2–1.1)	Age, smoking, and study centre	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Kogevinas *et al.* (2003) Re-analysis of 11 population-based studies Germany, France, Italy, Greece, Denmark, Spain, 1976–96	Bladder	3346 incident male cases, age 30–79 yr	6840 population-based or hospital controls individually or frequency-matched on age group and geographic area	Lifetime occupational history	Leather workers	48	1.3 (0.9–1.9)	Age, smoking, and study centre	Authors reported that risks were higher in studies conducted in 1990s vs 1980s
Samanic *et al.* (2008) Hospital-based Spain 1998–2000	Bladder carcinoma or in situ (1880–1889) (2337)	1219 incident cases (1067 men, 152 women, 84% participation) from 18 hospitals, age 21–80 yr	1465 controls (1105 men, 166 women, 88% participation) from the same hospitals with unrelated diseases and matched on sex, age, race/ethnicity, and hospital	Computer Assisted Interview (CAPI)	Leather, tanning and finishing Overall < 10 yr ≥ 10 yr	 28 10 18	 0.8 (0.4–1.3) 0.9 (0.4–2.2) 0.7 (0.3–1.4)	Age, region, smoking, other high-risk occupation	

CI, confidence interval; OR, odds ratio; yr, year or years; SES, socioeconomic status

Table 2.6 Other case–control studies with results for shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Mikoczy *et al.* (1996) Nested case–control study Sweden 1900–89	Pancreas, lung, soft tissue sarcoma	68 cases occurred among a cohort of 2487 workers from 3 Swedish tanneries	178 controls, 3 per case, matched on age and selected using incidence-density sampling from the same cohort	Exposure assigned by an occupational hygienist and long-term employees based on work histories	Leather dust: Pancreas Lung Soft tissue sarcoma	 8 8 NR	 7.2 (1.4–35.9) 0.7 (0.2–2.1) 3.8 (0.3–48.0)	Age, sex, and plant	All 4 pancreas cases & 1/11 controls exposed to vegetable dust No "noteworthy" associations reported for stomach, kidney, or bladder
Costantini *et al.* (2001) Multicentre (12 areas) population-based study Italy 1991–93	Lymphatic and haematopoietic cancers	Incident cases age 20–74 diagnosed during 1991–93. Composed of 811 male and 639 female NHL cases, 193 male and 172 female Hodgkin disease cases, and 383 male and 269 female leukaemia cases	1779 controls randomly selected from the general population frequency-matched on sex and age group	Interview at home to collect detailed occupational history and exposure to solvents and pesticides	Shoe makers and leather goods makers: Men– NHL and CLL Hodgkin disease All leukaemia	 30 3 7	 1.0 (0.5–1.9) 1.2 (0.3–4.0) 0.9 (0.3–2.2)	Age	Detailed results not presented for women

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Terry *et al.* (2005) Population-based USA & Canada 1986–89	Leukaemia	811 incident cases from a multisite study	637 controls recruited through random-digit dialling with frequency-matching on age, sex, race, and region	Telephone interview to gather information on employment and duration in 27 occupations	Leather/shoe industry or shoe repair (1+ yr) All leukaemia AML		 0.7 (0.3–1.5) 0.6 (0.3–1.5)	Age, sex, race, region, smoking, education, proxy response	Overall 84% response from cases, 34% from proxies. Overall 66% reponse rate with 13% surrogate respondents
Forand (2004) USA 1981–87	Leukaemia (204–208)	36 incident cases during 1981–90 among men 65 yr or older, residing in the town of Union and deceased as of August 1997	144 controls (all men) were matched by death certificate for year of death and year of birth (± 1 yr)	Occupation and employer determined from death certificates	Employment in boot & shoe industry AML Leukaemia	 13 4	 1.5 (0.7–3.1) 1.2 (0.3–4.3)	Matching on date of birth and death	

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; NHL, non-hodgkin leukaemia; NR, not reported; OR, odds ratio; yr, year or years

the prevalence of leather work in the source population.]

Results of descriptive studies from the United Kingdom and the Nordic countries are presented in Table 2.1. High relative risks were observed, particularly when presenting results for adenocarcinoma (Acheson *et al.*, 1970a, 1982). Relative risks in more recent studies are somewhat lower, but still significantly elevated (Acheson *et al.*, 1982; Olsen, 1988; Andersen *et al.*, 1999).

A large excess was reported in the pooled English and Florence cohorts, based on 12 and one cases observed, respectively (Fu *et al.*, 1996). The risk of sinonasal cancer was associated with probable exposure to leather dust in the English cohort (Fu *et al.*, 1996), and the excess was reported to be greatest in the finishing area in the earlier report on the English cohort (Pippard & Acheson, 1985). Results for sinonasal cancer were not reported for the Russian and American shoe-manufacturing cohorts (Bulbulyan *et al.*, 1998; Lehman & Hein, 2006). The US cohort study reported there was 'no evidence of any significant level of exposure to leather dust.' No sinonasal cancer cases were reported in any of the three proportionate mortality ratio (PMR) studies. There were 2.2 and 1.9 expected cases in the studies of Decouflé & Walrath (1983) and Walrath *et al.* (1987), respectively. Expected numbers were not reported for Garabrant & Wegman (1984), see Table 2.2.

Fourteen sinonasal case–control studies and one pooled re-analysis of seven European studies were reviewed. Twelve of the 14 studies observed evidence of an excess of sinonasal cancer, although sometimes based on very small numbers. The largest odds ratios were observed in the Italian studies, with odds ratios in the range of 3.5 (95%CI: 0.6–2.3) (Magnani *et al.*, 1993) to 121 (95%CI: 17.3–844) for heavy leather dust exposure (Merler *et al.*, 1986). In addition, two studies reported an infinite risk (Cecchi *et al.*, 1980 with seven cases and zero controls; Bimbi *et al.*, 1988 with three cases and zero controls). Excesses were also observed in studies from Sweden (Hardell *et al.*, 1982), Japan (Shimizu *et al.*, 1989), Germany (Bolm-Audorff *et al.*, 1989, 1990), and France (Luce *et al.*, 1992, 1993). The only non-positive studies were from the USA (Brinton *et al.*, 1984) and Canada (Teschke *et al.*, 1997), the only North American studies. The pooled re-analysis of European case–control studies observed increased risks associated with leather dust exposure among both men (OR, 1.9; 95%CI: 1.1–3.4) and women (odds ratio [OR], 2.7; 95%CI: 0.8–9.4), see Table 2.3.

Relative risks (RR) for adenocarcinoma were consistently high in descriptive (Acheson *et al.*, 1970b, 1982) and case–control studies (Cecchi *et al.*, 1980; Merler *et al.*, 1986; Comba *et al.*, 1992a; 't Mannetje *et al.*, 1999a). However, smaller excess risks were also observed in the few cases where squamous cell carcinoma results were presented (Shimizu *et al.*, 1989; Luce *et al.*, 1992, 1993; 't Mannetje *et al.*, 1999a).

In reviewing trends from Northamptonshire, the United Kingdom, Acheson *et al.* (1982) noted that the majority of cases had been employed in the departments with the most dusty operations, and that they had much higher risk compared to other operatives (RR, 4.5; 95%CI: 2.8–6.8). The retrospective cohort study of workers employed in the British boot and shoe industry also observed the highest risks among workers employed in the jobs with the highest exposure to leather dust (Pippard & Acheson, 1985). This was also observed in the update of the British cohort for the pooled analysis (Fu *et al.*, 1996). An increased risk among workers with the highest leather dust exposure was also observed in case–control studies that reported results for leather dust exposure (Merler *et al.*, 1986; Luce *et al.*, 2002). Most other case–control studies did not provide details regarding leather dust exposure, although Loi *et al.* (1989) did report that four of five leather workers were milling-machine operators, a group thought to have high leather dust exposure. In a pooled analysis of European

studies 't Mannetje *et al.* (1999a) observed an excess of adenocarcinoma (OR, 3.0; 95%CI: 1.3–6.7) as well as a possible increase for squamous cell carcinoma (OR, 1.5; 95%CI: 0.7–3.0).

2.2 Other respiratory cancers

None of the cohort or PMR studies reported results for the pharynx alone (Table 2.2). Among the three US PMR studies, Decouflé & Walrath (1983) and Walrath *et al.* (1987) observed slightly more cases than expected, but Garabrant & Wegman (1984) observed slightly less cases than expected. Tarvainen *et al.* (2008) observed an excess of oral and pharyngeal cancer among shoe makers in Finland based on only two cases. Gustavsson *et al.* (1998) observed an excess risk of squamous cell cancer associated with leather dust for both oral (OR, 2.2; 95%CI: 0.5–8.7) and pharyngeal (OR, 2.8; 95%CI: 0.8–10.2) cancer. Laforest *et al.* (2000) found no association between exposure to leather dust and squamous cell carcinoma of the hypopharynx. Boffetta *et al.* (2003) did not report separate results for the pharynx, but observed an excess of carcinomas of the larynx and hypopharynx among shoe finishers, but not shoe makers or repairers, see Table 2.4.

No excesses of cancer of the larynx were observed in the updated English or Italian cohorts or the three PMR studies (Table 2.2). Results for cancer of the larynx were not reported in the Russian or US cohorts. Gustavsson *et al.* (1998) observed an excess risk of squamous cell carcinoma of the larynx associated with leather dust exposure (OR, 2.1; 95%CI: 0.7–6.6). Laforest *et al.* (2000) found no association (OR, 0.9; 95%CI: 0.6–1.3) between exposure to leather dust and squamous cell carcinoma of the larynx. Boffetta *et al.* (2003) observed an excess of carcinoma of the larynx among shoe finishers (OR, 4.4; 95%CI: 1.0–18.8) that was not associated with duration of employment.

No excesses of lung cancer were observed in the updated English or Italian cohorts (Fu *et al.*, 1996). An excess was observed among men, but not among women in the Russian cohort (Bulbulyan *et al.*, 1998). The excess was limited to workers exposed to non-solvents who were also identified as having potential exposure to leather dust. An excess of lung cancer among both men and women was observed in the US cohort, which was not related to duration of employment (Lehman & Hein, 2006). Using indirect methods, the authors estimated that part, but not all, of the excess could be due to increased smoking rates among blue-collar workers. Although a small, but significant excess of lung cancer was observed among men (PMR, 1.2; $P < 0.05$) in Decouflé & Walrath (1983), no such excess was observed among women in the same study or among either sex in the other two PMR studies. In a pooled analysis of two German case–control studies, an excess risk for lung cancer among both male and female shoe workers was observed (Jöckel *et al.*, 2000). An excess was also observed in a a small Argentine case–control study (Matos *et al.*, 2000).

2.3 Leukaemia

Early studies reported in the previous *IARC Monograph* identified an unusually high prevalence of leukaemia and aplastic anaemia among shoe workers exposed to benzene in both Italy and Turkey (Aksoy *et al.*, 1974, 1976; Vigliani, 1976; Vigliani & Forni, 1976; Aksoy & Erdem, 1978). An excess was also identified in the Italian cohort study where benzene exposures were reported to be very high until 1963 when regulations were changed (Paci *et al.*, 1989; Fu *et al.*, 1996). An excess of leukaemia was observed among workers in the Russian cohort compared to the general population, and all five were in the highest solvent-exposed group (Bulbulyan *et al.*, 1998). All five of these cases were employed before 1960 when co-exposure to benzene was possible.

No excess was observed in the updated English cohort (Fu *et al.*, 1996). No excess of leukaemia was observed in the US cohort study (Lehman & Hein 2006). However, benzene was not detected in industrial hygiene surveys for the US study and "company management asserted that benzene had never been present in the solvents used at either of the plants." No excesses were observed in the three US PMR studies. Andersen *et al.* (1999) also did not observe an excess in the Nordic Census to tumour registry linkage study. More recent case–control studies, including a large, multicentre Italian study with cases diagnosed during 1991–93, have not observed an excess risk for leukaemia associated with employment in the leather industries (Costantini *et al.*, 2001; Forand, 2004; Terry *et al.*, 2005).

2.4 Cancer of the bladder

An excess of cancer of the bladder was not observed in the updated British, Italian, or US cohorts (Fu *et al.*, 1996; Lehman & Hein, 2006). A significant excess of cancer of the bladder was observed among women shoe workers (PMR, 2; $P < 0.05$) in Decouflé & Walrath (1983). However, no excess was observed among men. No excess of cancer of the bladder among either sex in another PMR study was found (Walrath *et al.*, 1987). Pukkala *et al.* (2009) observed a slight excess in the Nordic Census to tumour registry linkage study (SIR, 1.08; 95%CI: 0.98–1.19).

Results for cancer of the bladder from 11 case–control studies are presented in Table 2.5. Two studies, both using broad definitions of leather work, observed strong evidence of an excess risk. Cole *et al.* (1972) observed an excess risk among leather-product workers. Schoenberg *et al.* (1984) observed an excess among men working with leather materials. Several studies observed very small excesses associated with leather work. Marrett *et al.* (1986) found a very weak association associated with leather dust. Schumacher *et al.* (1989) found very weak evidence of an excess risk associated with the leather industry, but not with leather dust. Kogevinas *et al.* (2003) observed a possible small excess among men from 11 European studies in a pooled re-analysis but 't Mannetje *et al.* (1999b) observed a decreased risk among women from the same studies. Other studies either observed no risk or a decreased risk for cancer of the bladder among leather workers. Silverman *et al.* (1983) did not observe an excess among either leather products workers or shoe repairers in Detroit, USA. Silverman *et al.* (1989) did not observe an excess among either leather processing workers from ten regions of the USA. Siemiatycki *et al.* (1994) and Teschke *et al.* (1997) found no evidence of an association with leather or shoe work. Samanic *et al.* (2008) also did not observe an excess for cancer of the bladder associated with leather industry workers in Spain. [The Working Group noted that the results of Silverman *et al.* (1983) and Marrett *et al.* (1986) were not adjusted for smoking.]

2.5 Other cancers

Excesses of other cancers have been observed in some studies, but no consistent pattern has emerged (Decouflé & Walrath, 1983; Garabrant & Wegman, 1984; Walrath *et al.*, 1987; Mikoczy *et al.*, 1996; Bulbulyan *et al.*, 1998).

2.6 Synthesis

There is consistent and strong evidence from both descriptive and case–control studies associating work in the boot and shoe industry with an increased risk of cancer of the nasal cavity and paranasal sinuses. Among those studies with histological classification of the tumours, very large excess risks were observed for sinonasal adenocarcinoma. When examined in case–control studies, the Brittish cohort study, and case series, this excess appears among workers with the highest leather dust exposure. There

is strong evidence that exposure to leather dust causes cancer of the nasal cavity and paranasal sinuses.

Clusters of leukaemia cases were reported among workers with benzene exposure in the shoe industries of Italy and Turkey in the 1970s. An excess was also observed in an Italian cohort study and among a subgroup of a Russian cohort where benzene exposure was likely to have occurred. A case–control study in Italy did not observe an excess in the industry after changes in industrial practices resulted in large reductions in benzene exposure. Benzene is already recognized as a cause of leukaemia, and is likely to be the explaination of the previous excess observed in the industry.

Several early studies reported an excess risk of bladder cancer among leather workers. Two case–control studies observed an association with the leather industry, but many more recent studies found little or no association with the leather industry when tanning was not considered. For other cancer sites, no consistent pattern of excess risk was observed or too little data was available to adequately assess causality with boot and shoe manufacturing.

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

See Section 4 of the *Monograph* on Wood Dust in this Volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of leather dust. Leather dust causes cancer of the nasal cavity and paranasal sinuses.

No data in experimental animals for the carcinogenicity of leather dust were available to the Working Group.

Leather dust is *carcinogenic to humans (Group 1)*.

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SILICA DUST, CRYSTALLINE, IN THE FORM OF QUARTZ OR CRISTOBALITE

Silica was considered by previous IARC Working Groups in 1986, 1987, and 1996 (IARC, 1987a, b, 1997). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Silica, or silicon dioxide (SiO_2), is a group IV metal oxide, which naturally occurs in both crystalline and amorphous forms (i.e. polymorphic; NTP, 2005). The various forms of crystalline silica are: α-quartz, β-quartz, α-tridymite, β-tridymite, α-cristobalite, β-cristobalite, keatite, coesite, stishovite, and moganite (NIOSH, 2002). The most abundant form of silica is α-quartz, and the term quartz is often used in place of the general term crystalline silica (NIOSH, 2002).

1.1 Identification of the agent

α-Quartz is the thermodynamically stable form of crystalline silica in ambient conditions. The overwhelming majority of natural crystalline silica exists as α-quartz. The other forms exist in a metastable state. The nomenclature used is that of α for a lower-temperature phase, and β for a higher-temperature phase. Other notations exist and the prefixes low- and high- are also used (IARC, 1997). The classification and nomenclature of silica forms are summarized in Table 1.1. For more detailed information, refer to the previous *IARC Monograph* (IARC, 1997).

1.2 Chemical and physical properties of the agent

Selected chemical and physical properties of silica and certain crystalline polymorphs are summarized in Table 1.1. For a detailed discussion of the crystalline structure and morphology of silica particulates, and corresponding physical properties and domains of thermodynamic stability, refer to the previous *IARC Monograph* (IARC, 1997).

1.3 Use of the agent

The physical and chemical properties of silica make it suitable for many uses. Most silica in commercial use is obtained from naturally occurring sources, and is categorized by end-use or industry (IARC, 1997; NTP, 2005). The three predominant commercial silica product categories are: sand and gravel, quartz crystals, and diatomites.

Table 1.1 Nomenclature, CAS numbers, and classification of silica forms with selected physical and chemical properties

Name	CAS No.	Basic Formula	Classification	Synonyms	Properties
Silica	7631-86-9	SiO_2	α-quartz, β-quartz; α-tridymite, β1-tridymite, β2-tridymite; α-cristobalite, β-cristobalite; coesite; stishovite; moganite		Structure: crystalline, amorphous, cryptocrystalline Molecular weight: 60.1 Solubility: poorly soluble in water at 20 °C and most acids; increases with temperature and pH Reactivity: reacts with alkaline aqueous solutions, with hydrofluoric acid (to produce silicon tetrafluoride gas), and catechol
Crystalline Silica					
Cristobalite	14464-46-1		α-cristobalite, β-cristobalite		
Quartz	14808-60-7		α-quartz, β-quartz	α-quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	Solubility: 6–11 μg/cm³ (6–11 ppm) at room temperature; slightly soluble in body fluids Thermodynamic properties: melts to a glass; coefficient of expansion by heat—lowest of any known substance
Tripoli	1317-95-9				
Tridymite	15468-32-3		α-tridymite, β1-tridymite, β2-tridymite		

From IARC (1997), NIOSH (2002), NTP (2005)

1.3.1 Sand and gravel

Although silica sand has been used for many different purposes throughout history, its most ancient and principal use has been in the manufacture of glass (e.g. containers, flat plate and window, and fibreglass). Sands are used in ceramics (e.g. pottery, brick, and tile), foundry (e.g. moulding and core, refractory), abrasive (e.g. blasting, scouring cleansers, sawing and sanding), hydraulic fracturing applications, and many other uses. Several uses require the material to be ground (e.g. scouring cleansers, some types of fibreglass, certain foundry applications). In some uses (e.g. sandblasting, abrasives), grinding also occurs during use. For a more complete list of end-uses, refer to Table 8 of the previous *IARC Monograph* (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 121 million metric tons (Dolley, 2009). The leading producers were the USA (30.4 million metric tons), Italy (13.8 million metric tons), Germany (8.2 million metric tons), the United Kingdom (5.6 million metric tons), Australia (5.3 million metric tons), France (5 million metric tons), Spain (5 million metric tons), and Japan (4.5 million metric tons).

1.3.2 Quartz crystals

Quartz has been used for several thousand years in jewellery as a gem stone (e.g. amethyst, citrine), and is used extensively in both the electronics and optical components industries. Electronic-grade quartz is used in electronic circuits, and optical-grade quartz is used in windows, and other specialized devices (e.g. lasers) (IARC, 1997).

1.3.3 Diatomites

Diatomites are used in filtration, as fillers (in paint, paper, synthetic rubber goods, laboratory absorbents, anti-caking agents, and scouring powders), and as carriers for pesticides. They impart abrasiveness to polishes, flow and colour qualities to paints, and reinforcement to paper. Other uses include: insulators, absorption agents, scourer in polishes and cleaners, catalyst supports, and packing material (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 2.2 million metric tons. The USA accounted for 35% of total world production, followed by the People's Republic of China (20%), Denmark (11%), Japan (5%), Mexico (4%), and France (3%) (Crangle, 2009).

1.4 Environmental occurrence

Keatite, coesite, stishovite, and moganite are rarely found in nature. The most commonly occurring polymorphs are quartz, cristobalite and tridymite, which are found in rocks and soil. These forms of silica can be released to the environment via both natural and anthropogenic sources (e.g. foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth). Some of these anthropogenic activities may cause transformation of one polymorph into another (NIOSH, 2002).

1.4.1 Natural occurrence

α-Quartz is found in trace to major amounts in most rock types (e.g. igneous, sedimentary, metamorphic, argillaceous), sands, and soils. The average quartz composition of major igneous and sedimentary rocks is summarized in Table 10 of the previous *IARC Monograph* (IARC, 1997). Quartz is a major component of soils, composing 90–95% of all sand and silt fractions in a soil. It is the primary matrix mineral in the metalliferous veins of ore deposits, and can also be found in semiprecious stones, such as amethyst, citrine, smoky quartz, morion, and tiger's eye (IARC, 1997).

Crystalline tridymite and cristobalite are found in acid volcanic rocks. Cristobalite also occurs in some bentonite clays, and as traces in diatomite. Although rarely found in nature, coesite and stishovite have been found in rocks that equilibrated in short-lived high-pressure environments (e.g. meteoritic impact craters), and keatite has been found in high-altitude atmospheric dusts, which are believed to originate from volcanic sources (IARC, 1997).

For a more detailed description of the natural occurrence of crystalline silica and its polymorphs in air, water and soil, refer to the previous *IARC Monograph* (IARC, 1997).

1.5 Human exposure

1.5.1 Exposure of the general population

Inhalation of crystalline silica during the use of commercial products containing quartz is thought to be the primary route of exposure for the non-occupationally exposed (i.e. general) population. Commercial products containing quartz include: cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar. No quantitative data on potential levels of exposurem during the use of these products were available at the time of

writing (WHO, 2000). The general population may also be exposed via ingestion of potable water containing quartz particles; however, quantitative data on concentrations of quartz in potable or other forms of drinking-water were again not available (IARC, 1997; WHO, 2000).

1.5.2 Occupational exposure

Because of the extensive natural occurrence of crystalline silica in the earth's crust and the wide uses of the materials in which it is a constituent, workers may be exposed to crystalline silica in a large variety of industries and occupations (IARC, 1997). Table 1.2 lists the main industries and activities in which workers could be exposed to crystalline silica. Included in this table are activities that involve the movement of earth (e.g. mining, farming, construction, quarrying), disturbance of silica-containing products (e.g. demolition of masonry and concrete), handling or use of sand- and other silica-containing products (e.g. foundry processes, such as casting, furnace installation and repair; abrasive blasting; production of glass, ceramics, abrasives, cement, etc.).

Estimates of the number of workers potentially exposed to respirable crystalline silica have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupational Exposure Survey (NOES), conducted during 1981–83, and the *County Business Patterns 1986*, NIOSH estimated that about 1.7 million US workers were potentially exposed to respirable crystalline silica (NIOSH, 2002). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that more than 3.2 million workers in the then 15 Member States of the European Union during 1990–93 were considered as occupationally exposed to respirable crystalline silica above background level (Kauppinen *et al.*, 2000). Nearly 87% of these workers were employed in 'construction' (n = 2080000), 'manufacture of other non-metallic mineral products' (n = 191000), 'other mining' (n = 132000), 'manufacture of pottery, china and earthenware' (n = 96000), 'manufacture of machinery except electrical' (n = 78000), 'iron and steel basic industries' (n = 68000), 'manufacture of fabricated metal products, except machinery and equipment' (n = 68000), and 'metal ore mining' (n = 55000). The countries with the highest number of potentially exposed workers were: Germany (1 million workers), the United Kingdom (580000 workers), Spain (400000 workers), Italy (250000 workers), the Netherlands (170000 workers), France (110000 workers), and Austria (100000 workers) (Kauppinen *et al.*, 2000; Mirabelli & Kauppinen, 2005; Scarselli *et al.*, 2008).

For representative data in the main industries where quantitative exposure levels were available in the published literature and/or where major occupational health studies had been conducted, refer to the previous *IARC Monograph* (IARC, 1997). These main industries include mines and quarries, foundries and other metallurgical operations, ceramics and related industries, construction, granite, crushed stone and related industries, sandblasting of metal surfaces, agriculture, and miscellaneous other operations (IARC, 1997). Data from studies and reviews on crystalline silica exposure published since the previous *IARC Monograph* are summarized below.

(a) Levels of occupational exposure

To estimate the number of US workers potentially exposed to high levels of crystalline silica and to examine trends in exposure over time, Yassin *et al.* (2005) analysed data contained in the OSHA Integrated Management Information System (IMIS) database. After exclusion of duplicate bulk and area samples, a total of 7209 personal sample measurements collected during

Table 1.2 Main activities in which workers may be exposed to crystalline silica

Industry/activity	Specific operation/task	Source material
Agriculture	Ploughing, harvesting, use of machinery	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal and non-metal, coal)	Ores and associated rock
Quarrying and related milling operations	Crushing stone, sand and gravel processing, monumental stone cutting and abrasive blasting, slate work, diatomite calcination	Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth
Construction	Abrasive blasting of structures, buildings Highway and tunnel construction Excavation and earth-moving Masonry, concrete work, demolition	Sand, concrete Rock Soil and rock Concrete, mortar, plaster
Glass, including fibreglass	Raw material processing Refractory installation and repair	Sand, crushed quartz Refractory materials
Cement	Raw materials processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production Abrasive products fabrication	Sand Tripoli, sandstone
Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, moulding, glaze or enamel spraying, finishing	Clay, shale, flint, sand, quartzite, diatomaceous earth
Iron and steel mills	Refractory preparation and furnace repair	Refractory material
Silicon and ferro-silicon	Raw materials handling	Sand
Foundries (ferrous and non-ferrous)	Casting, shaking out Abrasive blasting, fettling Furnace installation and repair	Sand Sand Refractory material
Metal products including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Shipbuilding and repair	Abrasive blasting	Sand
Rubber and plastics	Raw material handling	Fillers (tripoli, diatomaceous earth)
Paint	Raw materials handling	Fillers (tripoli, diatomaceous earth, silica flour)
Soaps and cosmetics	Abrasive soaps, scouring powders	Silica flour
Asphalt and roofing felt	Filling and granule application	Sand and aggregate, diatomaceous earth
Agricultural chemicals	Raw material crushing, handling	Phosphate ores and rock
Jewellery	Cutting, grinding, polishing, buffing	Semiprecious gems or stones, abrasives
Dental material	Sandblasting, polishing	Sand, abrasives
Automobile repair	Abrasive blasting	Sand
Boiler scaling	Coal-fired boilers	Ash and concretions

From IARC, 1997

2512 OSHA inspections during 1988–2003 were analysed. The findings suggest that geometric mean crystalline silica exposure levels declined in some high-risk construction industries during the period under study, and revealed a significant decline when compared with silica exposure levels found in a previous study by Stewart & Rice (1990). Geometric mean airborne silica exposure levels among workers in the following industries were significantly lower in 1988–2003

than in 1979–87: general contractor industry (0.057 mg/m^3 versus 0.354 mg/m^3), bridge-tunnel construction industry (0.069 mg/m^3 versus 0.383 mg/m^3), and stonework masonry industry (0.065 mg/m^3 versus 0.619 mg/m^3). Silica exposures in the grey-iron industry also declined by up to 54% for some occupations (e.g. the geometric mean for "furnace operators" in 1979–87 was 0.142 mg/m^3 versus 0.066 mg/m^3 in 1988–2003). [The Working Group noted that exposure levels may not have decreased globally.]

Table 1.3 presents the more recent studies that assessed the levels of respirable crystalline silica in a range of industries and countries. Other recent exposure studies that did not measure the respirable crystalline silica components are presented below.

(b) Mines

As part of a cohort mortality study follow-up in four tin mines in China, Chen *et al.* (2006) developed quantitative exposure estimates of silica mixed dust. Workers in the original cohort were followed up from the beginning of 1972 to the end of 1994. Cumulative exposure estimates were calculated for each worker using their mine employment records and industrial hygiene measurements of airborne total dust, particle size, and free silica content collected since the 1950s. Total dust concentrations of the main job titles exposed were found to have declined from about 10–25 mg/m^3 in the beginning of the 1950s to about 1–4 mg/m^3 in the 1980s and 1990s. The respirable fraction of total dust was estimated to be 25 ± 4%, and the respirable crystalline silica concentration was estimated to be 4.3% of the total mixed mine dust

Tse *et al.* (2007) conducted a cross-sectional study to investigate the prevalence of accelerated silicosis among 574 gold miners in Jiangxi, China. Using occupational hygiene data abstracted from government documents and bulk dust data from a study in another gold mine in the region, the estimated mean concentration of respirable silica dust were reported as 89.5 mg/m^3 (range, 70.2–108.8 mg/m^3). According to government documents, the total dust concentration in underground gold mining was in the range of 102.6–159 mg/m^3 (average, 130.8 mg/m^3), and the fraction of silica in total dust was around 75.7–76.1%. No data on the proportion of respirable dust were available.

To determine dose–response relationships between exposure to respirable dust and respiratory health outcomes, Naidoo *et al.* (2006) used historical data (n = 3645) and current measurements (n = 441) to characterize exposure to respirable coal mine dust in three South African coal mines. Jobs were classified into the following exposure zones: face (directly involved with coal extraction), underground backbye (away from the coal mining face), and work on the surface. Based on the 8-hour full-shift samples collected respectively, mean respirable dust concentrations in Mines 1, 2, and 3, were as follows: 0.91 mg/m^3 (GSD, 3.39; mean silica content, 2.3%; n = 102), 1.28 mg/m^3 (GSD, 2.11; mean silica content, 1.4%; n = 63), and 1.90 mg/m^3 (GSD, 2.23; mean silica content, 2.7%; n = 73) at the face; 0.48 mg/m^3 (GSD, 2.97; mean silica content, 1.48%; n = 30), 0.56 mg/m^3 (GSD, 3.71; mean silica content, 1.35%; n = 47), and 0.52 mg/m^3 (GSD, 4.06; mean silica content, 0.9%; n = 41) in the backbye zone; and, 0.31 mg/m^3 (GSD, 3.52; mean silica content, 0.95%; n = 8), 0.15 mg/m^3 (GSD, 3.56; n = 6), and 0.24 mg/m^3 (GSD, 7.69; mean silica content, 0.64%; n = 11) in the surface zone. Based on the historical data, overall geometric mean dust levels were 0.9 mg/m^3 (GSD, 4.9), 1.3 mg/m^3 (GSD, 3.3), and 0.5 mg/m^3 (GSD, 5.6) for Mines 1, 2, and 3, respectively.

(c) Granite-quarrying and -processing, crushed stone, and related industries

Bahrami *et al.* (2008) described the personal exposure to respirable dust and respirable quartz in stone-crushing units located in western Islamic Republic of Iran. A total of 40 personal samples

Table 1.3 Respirable crystalline silica concentrations in various industries worldwide

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Mines				
Hayumbu *et al.* (2008), copper mines, the Zambia		Arithmetic mean (SD; range)		Cross-sectional dust exposure assessment; bulk and personal respirable samples; NIOSH method 0600 for gravimetric analysis of respirable dust; NIOSH method 7500 for quartz analysis of bulk and respirable samples; mean personal sampling time: 307 minutes (Mine 1) and 312 minutes (Mine 2)
	Mine 1	0.14 (0.2; 0–1.3)	101	
	Mine 2	0.06 (0.06; 0–0.3)	102	
Weeks & Rose (2006), metal and non-metal mines, USA, 1998–2002		Arithmetic mean (GM)		Mine Safety and Health Administration compliance data from 4726 mines; 8-hour full-shift personal air samples; gravimetric analysis of respirable dust; NIOSH method 7500 for silica analysis; arithmetic and geometric mean exposure calculated and classified by occupation, mine, and state
	Strip and open pit mines	0.047 (0.027)	13702	
	Mills or preparation plants	0.045 (0.027)	1145	
	Underground mines	0.050 (0.029)	1360	
	Overall	0.047 (0.027)	16207	
Bråtveit *et al.* (2003) underground small-scale mining, United Republic of Tanzania, 2001		Geometric mean (GSD)		Personal dust sampling (respirable and total dust) on 3 consecutive day shifts; sampling time varied between 5 and 8 hours; gravimetric analysis of respirable and total dust; NIOSH method 7500 for silica analysis
	Drilling, blasting, and shovelling	2.0 (1.7)	6	
	Shovelling and loading of sacks	1.0 (1.5)	3	
	Overall	1.6 (1.8)	9	
Park *et al.* (2002) diatomaceous earth mining and milling, California, USA, 1942–94	Mines and mills	Arithmetic mean 0.29 Cumulative exposure (mg/m^3–yr) 2.16	NR	Re-analysis of data from a cohort of 2342 California diatomaceous earth workers; mean concentration of respirable crystalline silica averaged over years of employment of cohort; crystalline silica content of bulk samples varied from 1–25%, and depended on process location
Mamuya *et al.* (2006) underground coal mining, United Republic of Tanzania; June–August 2003 and July–August 2004		Geometric mean (GSD)		Personal dust samples collected during two periods in 2003 and 2004; 134 respirable dust samples collected and analysed gravimetrically; 125 samples analysed for quartz using NIOSH method 7500
	Development team	0.073 (11.1)	56	
	Mine team	0.013 (2.97)	45	
	Transport team	0.006 (1.84)	11	
	Maintenance team	0.016 (11.05)	13	
	Overall	0.027 (8.18)	125	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Granite-quarrying and -processing, crushed stone, and related industries				
Wickman & Middendorf (2002) Granite–quarrying, Georgia, USA; May 1993–February 1994	Granite sheds	Arithmetic mean (SD) 0.052 (0.047)	40	Exposure assessment surveys in 10 granite sheds to measure compliance; full-shift respirable dust samples in workers' breathing zone and area samples; gravimetric analysis of respirable dust; crystalline silica analysis using OSHA ID 142; TWA exposures calculated
Brown & Rushton (2005a) Industrial silica sand, United Kingdom, 1978–2000	Quarries	Unadjusted geometric mean (GSD) 0.09 (3.9)	2429 (personal) 583 (static)	Samples collected by companies as part of routine monitoring programme; gravimetric analysis; silica content measured by Fourier transform infrared spectrophotometry until 1997 and by X-ray diffraction thereafter; personal and static measurements combined into one data set
Gottesfeld *et al.* (2008) Stone–crushing mills, India, 2003 (initial phase), 2006 and 2007 (post-implementation of engineering controls)		Arithmetic mean (SD)		Bulk and personal air samples collected; silica analysis using NIOSH method 7500; NIOSH method 0500 for respirable particulates used in 2003
	Prior to water-spray controls (2003)	Cristobalite, 0.09 (0.08)	[5]	
		Quartz, 0.25 (0.12)	[5]	
	After water-spray controls			
	Monsoon season (winter 2007)	Cristobalite, 0.02 (0.01)	[18]	
		Quartz, 0.01 (0.01)	[18]	
	Dry season (summer 2006)	Cristobalite, 0.03 (0.03)	[27]	
		Quartz, 0.06 (0.12(	[27]	
Yingratanasuk *et al.* (2002) Stone carvers, Thailand, 1999–2000		Arithmetic mean	148 (total number of samples)	Cross-sectional study design; full-shift (8-hour) personal dust samples; respirable dust analysed gravimetrically; silica analysis by infrared spectrophotometry
	Carvers (Site 1)	0.22		
	Pestle makers (Site 1)	0.05		
	Mortar makers (Site 2)	0.05		
	Mortar makers (Site 3)	0.88		

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Rando *et al.* (2001) Industrial sand industry, North America, 1974–98	Sand-processing plants	Geometic mean 0.042 (overall)	14249	Exposure estimates created for a longitudinal and case-referent analysis of a cohort of industrial sand workers; gravimetric analysis of total dust; silica analysis by X-ray diffraction spectroscopy
Yassin *et al.* (2005) Stonework masonry, USA, 1988–2003		Geometric mean (GSD)		Analysis of personal silica measurements ($n = 7209$) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	All occupations	0.065 (0.732)	274	
Foundries				
Andersson *et al.* (2009) Iron foundry, Sweden, April 2005–May 2006		Geometric mean (GSD)		Respirable dust, quartz, cristobalite, trydimite samples collected on 2 consecutive workdays for shift and daytime workers; gravimetric analysis conducted using modified NIOSH method; respirable quartz and cristobalite analysed using modified NIOSH method 7500
	Caster	0.020 (1.8)	22	
	Core Maker	0.016 (2.3)	55	
	Fettler	0.041 (2.9)	115	
	Furnace and ladle repair	0.052 (3.7)	33	
	Maintenance	0.021 (2.6)	26	
	Melter	0.022 (2.0)	49	
	Moulder	0.029 (2.6)	64	
	Sand mixer	0.020 (2.3)	14	
	Shake out	0.060 (1.7)	16	
	Transportation	0.017 (2.6)	13	
	Other	0.020 (2.0)	28	
	All occupations	0.028 (2.8)	435	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Yassin *et al.* (2005) Grey–iron foundry, USA 1988–2003		Geometric mean (GSD)		Analysis of personal silica measurements (n = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	Spruer	0.154 (0.100)	22	
	Hunter operator	0.093 (1.144)	10	
	Charger	0.091 (0.999)	8	
	Core maker	0.078 (1.033)	89	
	Grinder	0.075 (0.821)	371	
	Molder	0.073 (0.910)	308	
	Abrasive blast operator	0.070 (0.821)	56	
	Sorter	0.067 (0.827)	23	
	Reline cupola	0.067 (0.725)	29	
	Furnace operator	0.066 (0.766)	47	
	Core setter	0.066 (0.671)	23	
	Craneman	0.066 (0.815)	16	
	Cleaning department	0.060 (0.879)	36	
	Inspector	0.057 (1.298)	21	
	Ladle repair	0.055 (0.829)	30	
Other metallurgical operations				
Føreland *et al.* (2008) Silicon carbide industry, Norway, November 2002–December 2003		Geometric mean	720 (total)	Exposure survey conducted in 3 silicon carbide plants; measurements collected to improve previously developed job–exposure matrix; sampling duration close to full shift (6–8 hours); 2 sampling periods of 2 work weeks; gravimetric analysis of respirable dust; silica analysis using modified NIOSH method 7500
	Cleaning operators (Plant A)	0.020 (quartz)		
	Mix operators (Plants A and C), charger/ mix and charger operators (Plant C)	0.008–0.013 (quartz)		
	All other jobs (Plants A, B and C)	< 0.005 (quartz)		
	Charger/mix operators (Plant C)	0.038 (cristobalite)		
Construction				
Tjoe-Nij *et al.* (2003) Construction, the Netherlands		Geometric mean (GSD)		Cross-sectional study design; repeated dust measurements (n = 67) on 34 construction workers; full-shift (6–8 hours) personal respirable dust sampling; gravimetric analysis of respirable dust; silica analysis by infrared spectroscopy (NIOSH method 7602); 8-h TWA concentrations calculated
	Concrete drillers and grinders	0.42 (5.0)	14	
	Tuck pointers	0.35 (2.8)	10	
	Demolition workers	0.14 (2.7)	21	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m^3)	Number of samples	Comments
Akbar-Khanzadeh & Brillhart (2002) Construction, USA	Concrete–finishing (grinding)	Arithmetic mean (SD) 1.16 (1.36)	49	Task-specific silica exposure assessment conducted as part of an OSHA Consultation Service in Ohio; gravimetric analysis of respirable samples using NIOSH method 0600; silica analysis using in-house method based on NIOSH method 7500 and OSHA ID 142
Verma *et al.* (2003)		Range (min–max)		Task-based exposure assessment conducted as part of an epidemiological study of Ontario construction workers; personal dust sampling and direct–reading particulate monitoring; gravimetric analysis of respirable dust using modified NIOSH method 0600; respirable silica analysis using modified NIOSH method 7500
	Labourers	0.10–0.15	20	
	Operating engineers	0.04–0.06	3	
	Carpenters, iron workers, masons, painters, terrazzo workers	below detectable limits	17	
Woskie *et al.* (2002) Heavy and highway construction, USA		Geometric mean (GSD)		Personal samples collected using the Construction Occupational Health Program sampling strategy; particulate samples analysed gravimetrically; quartz analysed by Fourier transform infrared spectrophotometry; duration of sampling—6 hours of an 8-hour working day
	Labourers	0.026 (5.9)	146	
	Miscellaneous trade	0.013 (2.8)	26	
	Operating engineers	0.007 (2.8)	88	
Flanagan *et al.* (2003) Construction, USA, August 2000–January 2001	Clean-up, demolition with hand-held tools, concrete cutting, concrete mixing, tuck-point grinding, surface grinding, sacking and patching concrete, and concrete-floor sanding	Geometric mean (GSD) 0.11 (5.21)	113	Respirable samples analysed gravimetrically using NIOSH method 0600; silica analysed by Fourier transform infrared spectrophotometry using NIOSH method 7602
Lumens & Spee (2001) Construction, the Netherlands		Geometric mean (GSD)		Personal air samples collected during field study at 30 construction sites; duration of sampling 3 to 4 hours; gravimetric analysis of respirable dust samples; silica analysis using NIOSH method 7500
	Recess miller	0.7 (3.3)	53	
	Demolition worker	1.1 (4.0)	82	
	Inner wall constructor	0.04 (2.6)	36	
	Overall	0.5 (5.6)	171	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Flanagan *et al.* (2006) Construction, USA, 1992–2002		Geometric mean (GSD)		Personal silica measurements collected as part of a silica-monitoring compilation project; data provided by 3 federal or state regulatory agencies (n = 827 samples), 6 university or research agencies (n = 491), and 4 private consultants or contractors (n = 134)
	Abrasive blasters, surface and tuck point grinders, jackhammers, rock drills	0.13 (5.9)	1374	
Akbar-Khanzadeh *et al.* (2007) Construction, USA		Arithmetic mean		Personal samples collected during grinding operations in a controlled field laboratory to evaluate the effectiveness of wet grinding and local exhaust ventilation; samples collected and analysed using NIOSH methods 0600 and 7500
	Uncontrolled conventional grinding	61.7	5 sessions	
	Wet grinding	0.896	7 sessions	
	Local exhaust ventilation grinding	0.155	6 sessions	
Bakke *et al.* (2002) Construction, Norway, 1996–99		Geometric mean (GSD)		Personal samples collected as part of exposure survey; sampling duration: 5 to 8 h; respirable dust analysed gravimetrically; silica analysed by NIOSH method 7500
	Tunnel workers	α-Quartz, 0.035 (5.0)	299	
Linch (2002) Construction, USA, 1992–98		TWA (8-hour)		Personal samples collected as part of NIOSH effort to characterize respirable silica exposure in construction industry; respirable dust collected and analysed according to NIOSH method 0600; silica analysed by NIOSH method 7500
	Abrasive blasting of concrete structures	2.8		
	Drilling concrete highway pavement	3.3		
	Concrete-wall grinding	0.26		
	Concrete sawing	10.0		
	Milling of asphalt	0.36		
Meijer *et al.* (2001) Construction, USA, 1992–93		Arithmetic mean		Personal samples of respirable dust and silica; gravimetric analysis of respirable dust; silica analysed by infrared spectrophotometry
	Concrete workers	0.06	96	
Miscellaneous operations				
Hicks & Yager (2006) Coal-fired power plants, USA		Arithmetic mean		Personal breathing zone samples collected during normal full shifts and analysed by NIOSH method 7500
	Normal production activities	0.048	108	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Shih *et al.* (2008)		Arithmetic mean		Exposures measured in a municipal waste incinerator during annual furnace relining; respirable dust collected and analysed by NIOSH method 0600; silica analysed by NIOSH method 7500
Furnace relining, Taiwan, China	Sandblasting	0.578	7	
	Bottom-ash cleaning	0.386	8	
	Wall demolishing	0.116	8	
	Relining	0.041	10	
	Grid repairing	0.042	14	
	Scaffold establishing	0.040	8	
	Others	0.082	8	
Zhuang *et al.* (2001)		Arithmetic mean		Special exposure survey conducted to compare results obtained from traditional Chinese samplers with nylon cyclones; gravimetric analysis of cyclone samples; silica analysis using X-ray diffraction
Pottery factories and metal mines, China, 1988–89	Pottery factories	0.116	54	
	Iron/copper mines	0.017	23	
	Tin mines	0.097	10	
	Tungsten mines	0.101	56	
Yassin *et al.* (2005)		Geometric mean (GSD)		Analysis of personal silica measurements (n = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
Several industries, USA, 1988–2003	Soap and other detergents	0.102 (0.757)	6	
	Testing laboratories services	0.099 (0.896)	53	
	Cut stone and stone products	0.091 (0.956)	405	
	General contractors	0.091 (0.900)	28	
	Coating engraving	0.075 (0.839)	75	
	Grey–iron foundries	0.073 (0.877)	1 760	
	Concrete work	0.073 (0.705)	94	
	Manufacturing explosives	0.070 (0.841)	9	
	Bridge-tunnel construction	0.070 (0.827)	91	
	Stonework masonry	0.065 (0.732)	274	
	Overall	0.073 (0.919)	7209	

GM, geometric mean; GSD, geometric standard deviation; IMIS, Integrated Management Information System; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OSHA; SD, standard deviation

and 40 area samples were collected and analysed by X-ray diffraction. Personal samples were collected after the installation of local exhaust ventilation, and area samples were collected inside the industrial units before (n = 20) and after (n = 20) the installation of local exhaust ventilation. Personal samples were collected from process workers (n = 12), hopper workers (n = 8), drivers (n = 11), and office employees (n = 9). Personal concentrations of respirable dust were as follows: process workers, 0.21 mg/m^3; hopper workers, 0.45 mg/m^3; and, drivers, 0.20 mg/m^3. Personal concentrations of respirable quartz were as follows: process workers, 0.19 mg/m^3; hopper workers, 0.40 mg/m^3; and, drivers, 0.17 mg/m^3. Based on the area samples, the average levels of total dust and respirable dust were 9.46 mg/m^3 and 1.24 mg/m^3, respectively. The amount of free silica in the stone was 85–97%.

Golbabaei *et al.* (2004) measured TWA concentrations of total dust, respirable dust, and crystalline silica (α-quartz) in a marble stone quarry located in the north-eastern region of the Islamic Republic of Iran. Full-shift (2 × 4-hour samples) personal breathing zone samples were collected and analysed using gravimetric and X-ray diffraction methods. The highest levels of total and respirable dust exposure were observed for workers in the hammer drill process area (107.9 mg/m^3 and 11.2 mg/m^3, respectively), and the cutting machine workers had the lowest levels of exposure (9.3 mg/m^3 and 1.8 mg/m^3, respectively). The highest concentrations of α-quartz in total and respirable dust were measured in hammer drill process workers (0.670 mg/m^3 and 0.057 mg/m^3, respectively).

In a NIOSH-conducted cohort mortality study of workers from 18 silica sand plants, Sanderson *et al.* (2000) estimated historical quartz exposures using personal respirable quartz measurements (collected during 1974–96) and impinger dust samples (collected in 1946). During 1974–96, a total of 4269 respirable dust samples were collected from workers performing 143 jobs at these 18 plants. Respirable quartz concentrations ranged from less than 1 to 11700 µg/m^3, with a geometric mean concentration of 25.9 µg/m^3. Over one-third of the samples exceeded the Mine Safety and Health Administration permissible exposure limit value for quartz (PEL, 10 mg/m^3/(%quartz + 2)), and half of the samples exceeded the NIOSH recommended exposure limit [at the time] (REL, 0.050 mg/m^3). Quartz concentrations varied significantly by plant, job, and year and decreased over time, with concentrations measured in the 1970s being significantly greater than those measured later.

(d) Foundries

Lee (2009) reported on exposures to benzene and crystalline silica during the inspection of a foundry processing grey and ductile iron. The facility consisted of two buildings: the main foundry where moulding, core-making, metal pouring, and shakeout took place; and, the finishing part of the site where grinding and painting was done. Personal sampling for crystalline silica was conducted in the grinding area, in casting shakeout, and in both the mould- and core-making operations. Eight-hour TWA concentrations of crystalline silica were in the range of 2.11–4.38 mg/m^3 in the grinding area (n = 4), 1.18–2.14 mg/m^3 in the shakeout area (n = 2), and 1.15–1.63 mg/m^3 in the core-maker area (n = 2). The 8-hour TWA concentration in the mould area was 0.988 mg/m^3.

(e) Construction

In a study of cement masons at six commercial building sites in Seattle, WA, USA, Croteau *et al.* (2004) measured personal exposures to respirable dust and crystalline silica during concrete-grinding activities to assess the effectiveness of a commercially available local exhaust ventilation (LEV) system. Levels were measured with and without LEV, one sample directly after the other. A total of 28 paired

samples were collected. The results showed that the application of LEV resulted in a mean exposure reduction of 92%, with the overall geometric mean respirable dust exposure declining from 4.5 to 0.14 mg/m^3. However, approximately one quarter of the samples collected while LEV was being used were greater than the OSHA 8–hour TWA PEL (22% of samples), and the American Conference of Governmental Industrial Hygiene (ACGIH) threshold limit value (26%) for respirable crystalline silica.

Rappaport *et al.* (2003) investigated exposures to respirable dust and crystalline silica among 80 workers in four trades (bricklayers, painters (when abrasive blasting), operating engineers, and labourers) at 36 construction sites in the Eastern and Midwestern USA. A total of 151 personal respirable air samples were collected and analysed using gravimetric and X-ray diffraction methods. Painters had the highest median exposures for respirable dust and silica (13.5 and 1.28 mg/m^3, respectively), followed by labourers (2.46 and 0.350 mg/m^3), bricklayers (2.13 and 3.20 mg/m^3), and operating engineers (0.720 and 0.075 mg/m^3). The following engineering controls and workplace characteristics were found to significantly affect silica exposures: wet dust suppression reduced labourers' exposures by approximately 3-fold; the use of ventilated cabs reduced operating engineers' exposures by approximately 6-fold; and, working indoors resulted in a 4-fold increase in labourers' exposures.

(f) Agriculture

Archer *et al.* (2002) assessed the exposure to respirable silica of 27 farm workers at seven farms in eastern North Carolina, USA. Four-hour personal breathing zone samples (n = 37) were collected during various agricultural activities and analysed for respirable dust, respirable silica, and percentage silica using gravimetric and X-ray diffraction methods. The overall mean respirable dust, respirable silica, and percentage silica values were 1.31 mg/m^3 (n = 37), 0.66 mg/m^3 (n = 34), and 34.4% (n = 34), respectively. The highest respirable dust and respirable silica concentrations were measured during sweet potato transplanting (mean, 7.6 and 3.9 mg/m^3, respectively; n = 5), and during riding on or driving an uncabbed tractor (mean, 3.1 and 1.6 mg/m^3, respectively; n = 13).

Nieuwenhuijsen *et al.* (1999) measured personal exposure to dust, endotoxin, and crystalline silica during various agricultural operations at ten farms in California, USA, between April 1995 and June 1996. A total of 142 personal inhalable samples and 144 personal respirable samples were collected. The highest levels of inhalable dust exposure were measured during machine-harvesting of tree crops and vegetables (GM, 45.1 mg/m^3 and 7.9 mg/m^3, respectively), and during the cleaning of poultry houses (GM, 6.7 mg/m^3). Respirable dust levels were generally low, except for machine-harvesting of tree crops and vegetables (GM, 2.8 mg/m^3 and 0.9 mg/m^3, respectively). The percentage of crystalline silica was higher in the respirable dust samples (overall, 18.6%; range, 4.8–23.0%) than in the inhalable dust samples (overall, 7.4%; range, not detectable to 13.0%).

(g) Miscellaneous operations

Harrison *et al.* (2005) analysed respirable silica dust samples (n = 47) from several Chinese workplaces (three tungsten mines, three tin mines, and nine pottery mines) to determine the effect of surface occlusion by alumino-silicate on silica particles in respirable dust. The average sample percentages of respirable-sized silica particles indicating alumino-silicate occlusion of their surface were: 45% for potteries, 18% for tin mines, and 13% for tungsten mines.

To provide a more precise estimate of the quantitative relationship between crystalline silica and lung cancer, 't Mannetje *et al.* (2002) conducted a pooled analysis of existing quantitative exposure data for ten cohorts exposed to silica

(US diatomaceous earth workers; Finnish and US granite workers; US industrial sand workers; Chinese pottery workers, and tin and tungsten miners; and South African, Australian, and US gold miners). Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligrams per cubic metre (mg/m^3) respirable crystalline silica. The median of the average cumulative exposure to respirable crystalline silica ranged from 0.04 mg/m^3 for US industrial sand workers to 0.59 mg/m^3 for Finnish granite workers. The cohort-specific median of cumulative exposure ranged from 0.13 mg/m^3–years for US industrial sand workers to 11.37 mg/m^3–years for Australian gold miners.

In a cross-sectional survey, Hai *et al.* (2001) determined the levels of respirable nuisance and silica dusts to which refractory brickworkers were exposed at a company in Ha Noi, Viet Nam. Respirable dust levels were in the range of 2.2–14.4 mg/m^3 at nine sample sites. The estimated free silica content of dust was 3.5% for unfired materials at the powder collectors (n = 8 samples), and 11.4% in the brick-cleaning area following firing (n = 1 sample).

Burgess (1998) investigated processes associated with occupational exposure to respirable crystalline silica in the British pottery industry during 1930–1995, and developed a quantitative job–exposure matrix. Exposure estimates were derived from 1390 air samples, the published literature, and unpublished reports of dust control innovations and process changes. In the matrix, daily 8-hour TWA airborne concentrations of respirable crystalline silica ranged from 0.002 mg/m^3 for pottery-support activities performed in the 1990s to 0.8 mg/m^3 for firing activities in the 1930s. Although exposure estimates within decades varied, median concentrations for all process categories displayed an overall trend towards progressive reduction in exposure during the 65 year span.

2. Cancer in Humans

2.1 Cancer of the lung

In the previous *IARC Monograph* (IARC, 1997) not all studies reviewed demonstrated an excess of cancer of the lung and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results had been expected. However, overall, the epidemiological findings at the time supported an association between cancer of the lung and inhaled crystalline silica (α-quartz and cristobalite) resulting from occupational exposure.

The current evaluation has a primary focus on studies that employed quantitative data on occupational exposures to crystalline silica dust (α-quartz and cristobalite). The establishment of exposure–response relationships not only provides critical evidence of causation, but the availability of quantitative exposures on crystalline silica and other exposures of relevance facilitates the accurate assessment of exposure–response relationships in the presence of potential confounders. In addition to the focus on quantitative exposure–response relationships, a summary of findings from eight published meta-analyses of lung cancer was also elaborated. Of these, the seven meta-analyses involving absolute risk summarize the information from the many studies that did not consider quantitative exposure–response relationships, while the eighth is a meta-analysis of exposure-response.

Findings from cohort studies are given in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.1.pdf, and those for the case–control studies are provided in Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.2.pdf. Given that there was concern by the previous IARC Working Group that different exposure settings (including the nature of the industry and the crystalline silica polymorph) may give rise to different (or

no) cancer risks, this evaluation is divided into sections based on the industrial setting where exposure to silica occurs. As with other evaluations, data from community-based studies are not included, although studies of persons with silicosis are.

2.1.1 Diatomaceous earth

Work in the diatomaceous earth industry is associated mainly with exposure to cristobalite rather than quartz, and, in the USA, is generally free of other potential confounding exposures apart from exposure to asbestos in a minority of locations. The first study of US diatomaceous earth workers revealed significant positive trends in lung cancer risk with both cumulative exposure to crystalline silica (semiquantitative) and duration of employment (Checkoway *et al.*, 1993). Owing to concerns with confounding from asbestos, estimates of asbestos exposure were developed (Checkoway *et al.*, 1996). Those with uncertain asbestos exposures were omitted from the analysis leading to the loss of seven lung cancer deaths. Among those with no asbestos exposure, the lung cancer standardized mortality ratios (SMR) for the two higher crystalline silica exposure groups were twice the magnitude of those for the two lowest exposure groups, although they were not significantly elevated. Rate ratios, with and without adjustment for asbestos exposure were very similar (within 2%), indicating that confounding due to asbestos was not an issue. Checkoway *et al.* (1997) provided findings from one of the two plants previously investigated but including 7 more years of follow-up as well as newly developed quantitative respirable crystalline silica exposures (Table 2.1 online). The lung cancer relative risks (RR) for the highest unlagged or 15-year exposure category were both significantly elevated. Trends for both unlagged and lagged exposure–response were of borderline significance. Rice *et al.* (2001) used the same cohort to examine risk, assessing the relationship between lung cancer mortality and respirable crystalline silica exposure using a variety of models. All except one model demonstrated statistical significance, and the trends of the predicted rate ratios with cumulative crystalline silica exposure were generally similar across models.

A small cohort study among Icelandic diatomaceous earth workers (Rafnsson & Gunnarsdóttir, 1997) provided findings that supported an effect of crystalline silica on lung cancer risk (SIR, 2.34; 95%CI: 0.48–6.85 for those who had worked 5 or more years). Smoking habits among the workers were reported to be similar to the general population.

2.1.2 Ore mining

Steenland & Brown (1995) updated a cohort of US gold miners previously studied (McDonald *et al.*, 1978; Table 2.1 online). Using quantitative estimates of cumulative exposure based on particle counts, no obvious evidence of exposure–response with lung cancer mortality was observed, nor were any of the exposure category SMRs elevated. In contrast, tuberculosis and silicosis mortality was elevated and exhibited an exposure–response relationship with crystalline silica exposure.

Gold miners were investigated in a South African cohort study (Hnizdo & Sluis-Cremer, 1991) and in case–control studies nested within that cohort study and within another South African gold miner cohort (Reid & Sluis-Cremer, 1996; Tables 2.1 and 2.2 online). In the Hnizdo & Sluis-Cremer, (1991) cohort study, lung cancer mortality was related to cumulative dust exposure when modelled as a continuous variable (respirable-surface-area–years) adjusting for smoking, as well demonstrating a monotonic increase with categories of cumulative exposures. There was also some indication of exposure–response in both case–control studies: RR, 1.12; 95%CI: 0.97–1.3 for Reid & Sluis-Cremer (1996),

and lung cancer mortality was elevated in the highest exposure group adjusting for smoking in the Hnizdo *et al.* (1997) study. [In this study, exposure to uranium did not confound the results.] [The Working Group noted the potential for confounding from radon, and also noted that the South African cohorts might overlap.]

McLaughlin *et al.* (1992) undertook a nested case–control study of lung cancer among the members of a prior cohort study by Chen *et al.* (1992) (Table 2.2 online). The study included workers from iron, copper, tungsten, and tin mines, and used quantitative estimates of crystalline silica dust and certain confounder exposures. Only tin miners showed a clear and substantial exposure–response relationship with the quantitative measures of crystalline silica cumulative exposure. The tin miners underwent further follow-up in a cohort study (Chen *et al.*, 2006) and a nested case–control study (Chen & Chen, 2002). Although the cohort study findings provided some overall indication of elevated lung cancer exposure–response mortality with cumulative dust exposure (Table 2.1 online), the findings were much less clear when presented by mine and silicosis status. In the nested case–control study (Table 2.2 online), there was evidence of exposure–response with cumulative total dust exposures. There was also evidence of a relationship between lung cancer mortality and cumulative arsenic exposure, but the high correlation between arsenic and crystalline silica levels prevented mutual adjustment, and left the etiological factor unclear. The same conclusions, more generally expressed, were reported in a simple ever/never exposed approach by Cocco *et al.* (2001), and were confirmed by Chen *et al.* (2007) adjusting for smoking and other confounding factors. Here, no relationship of lung cancer mortality with cumulative crystalline silica exposure was noted for the tungsten mines, nor was any evidence for the iron and copper mines adjusting for radon. [The Working Group noted that crystalline silica exposures were very low in the iron and copper mines.] For the tin mines, no adjustment for arsenic could be made because of its collinearity with crystalline silica exposure, but in the overall group, adjusting for smoking, arsenic, polyaromatic hydrocarbons (PAHs), and radon, no exposure–response for cumulative crystalline silica exposure emerged either by quintile or through the use of a continuous predictor. This was especially true when the iron/copper mines were removed for reason of having poorer data, when the trend tended towards lower risk with increasing crystalline silica exposure.

Carta *et al.* (2001) examined 724 compensated silicotics with radiographic indication of 1/0 or greater small opacities on the International Labor Organization scale who had worked at Sardinian lead and zinc mines, brown coal mines, and granite quarries. Using quantitative estimates of cumulative exposure to respirable crystalline silica dust and radon, the exposure–response was studied in a cohort study and a nested case–control study of 34 lung cancer cases (Tables 2.1 and 2.2 online). Little evidence of a trend with crystalline silica exposure was observed in either study component (after controlling for smoking, airflow obstruction, radon, and severity of silicosis in the case–control study). A clear relationship emerged with exposure to radon in the case–control study. [The Working Group noted that this study was small.]

2.1.3 Ceramics

A case–control study of Chinese pottery workers showed evidence of elevated risk for lung cancer with exposure to crystalline silica dust, although no obvious exposure–response was seen in the three higher exposure categories (McLaughlin *et al.*, 1992; Table 2.2 online). This study was nested within the cohort analysis by Chen *et al.* (1992). Although reported exposure to asbestos was to be minimal, the workers were exposed to PAHs, and in a separate analysis

there were non-significant elevations in lung cancer risk with increasing cumulative exposure to PAHs. This was confirmed in the follow-up analysis by Chen *et al.* (2007) that found that the pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs in the analysis led to the crystalline silica exposure relative risk of 1.1 (95%CI: 1.02–1.12) dropping to 1.0 (95%CI: 0.96–1.09). [The Working Group noted that in the prior analysis of the Chinese ceramics data by McLaughlin *et al.* (1992), adjusting for PAHs slightly raised rather than reduced the crystalline silica exposure relative risks. The correlation between the crystalline silica and PAH exposures was reported as 0.56.]

Another case–control study of pottery workers with quantitative crystalline silica dust exposures was from the United Kingdom (Cherry *et al.*, 1998). This analysis, which was restricted to ever smokers but adjusted for smoking amount and ex-smoking, showed a significantly elevated risk of lung cancer mortality with increasing average intensity of exposure, but not with cumulative exposure. No confounders, apart from smoking, were noted in this report.

Ulm *et al.* (1999) looked at workers in the German ceramics industry, as well as the stone and quarrying industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. No relationship of lung cancer mortality risk with cumulative exposure, average intensity, nor peak exposure was seen in the ceramic worker subset nor overall. [The Working Group noted that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.]

2.1.4 Quarries

In an extension of the Vermont granite workers study by Costello & Graham (1988), Attfield & Costello (2004) both lengthened the follow-up from 1982 to 1994, and developed and analysed quantitative crystalline silica dust exposures (Table 2.1 online). The exposures were noteworthy for being developed from environmental surveys undertaken throughout the period of the study. However, information on smoking and silicosis status was lacking, although confounding from other workplace exposures was likely to have been minimal or non-existent. The results showed a clear trend of increasing risk of lung cancer mortality with increasing cumulative respirable crystalline silica exposure up until the penultimate exposure group. [The Working Group noted that the findings were heavily dependent on the final exposure group; when it was included, the models were no longer statistically significant.] Graham *et al.* (2004) undertook a parallel analysis of the same data as Attfield & Costello (2004), but did not use quantitative exposures, and adopted essentially the same analytical approach as in their 1998 study. They concluded that there was no evidence that crystalline silica dust exposure was a risk factor for lung cancer, their main argument being that lung cancer risks were similar by duration and tenure between workers hired pre-1940 and post-1940 – periods before and following the imposition of dust controls when the crystalline silica dust levels were very different.

As noted above, Ulm *et al.* (1999) looked at workers in the German stone and quarrying industry (includes some sand and gravel workers), as well as the ceramics industry (Table 2.2 online). The study was based solely on those without silicosis, as assessed using radiographic appearances. Neither cumulative exposure, average intensity, nor peak exposure showed a relationship with lung cancer risk in the stone and quarry worker subset, nor overall. [The Working Group noted

that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.] Another study of German stone and quarry workers found an excess of lung cancer (SMR, 2.40), but no relationship between lung cancer mortality and crystalline silica exposure. [The Working Group noted that the cohort study included only 440 individuals with 16 lung cancer cases. It was also restricted to those with silicosis, which was likely to lead to a lack of low exposures, a consequent limited exposure range, and low study power.]

Among studies that did not use quantitative estimates of crystalline silica exposure, that by Koskela *et al.* (1994) is of interest because it reported that the workers had little exposure to possible confounding exposures. The risk of lung cancer was significantly elevated among those with longer duration of exposure and longer latency ($P < 0.05$). Guénel *et al.* (1989) also found an excess of lung cancer among stone workers after adjustment for smoking, but this was not the case in a study of slate workers by Mehnert *et al.* (1990).

2.1.5 Sand and gravel

Confounding from other workplace exposures is minimal in sand and gravel operations. There are three main studies of sand and gravel workers, two in North America and one in the United Kingdom. The North American studies appear to arise from the same population of workers although there is no published information on their overlap, if any. Using the basic information from the McDonald *et al.* (2001) cohort study of nine North American sand and gravel workers, Hughes *et al.* (2001) reported significant exposure–response of lung cancer with quantitative estimates of cumulative respirable crystalline silica exposures and other related indices. McDonald *et al.* (2005) examined a slightly smaller subset of the cohort described by McDonald *et al.* (2001) based on an extended update at eight of the nine plants, and also undertook a nested case–control study. Risk of lung cancer increased monotonically with unlagged cumulative exposure ($P = 0.011$), but 15-year lagged cumulative exposures provided a slightly better fit ($P = 0.006$) (Table 2.2 online). These findings were basically similar to those obtained by Hughes *et al.* (2001) using the larger cohort and shorter follow-up time. McDonald *et al.* (2005) reported that average exposure intensity, but not years employed, showed a relationship with lung cancer risk ($P = 0.015$).

Steenland & Sanderson (2001) studied workers in 18 sand and gravel companies in the same trade organization as the nine included in the McDonald *et al.* (2001) study (Table 2.1 online). They, too, employed quantitative estimates of exposure derived from company records, and found indications of a relationship with lung cancer mortality, most strongly in the subset that had worked 6 or more months in the industry ($P < 0.06$). Further analysis using a nested case–control approach found marginal evidence of exposure–response using quartiles of cumulative exposure ($P = 0.04$), but stronger evidence with average intensity ($P = 0.003$). [The Working Group noted that a sensitivity analysis of the effect of smoking in this cohort (Steenland & Greenland, 2004) led to an adjusted overall SMR estimate of 1.43 (95% Monte Carlo limits: 1.15–1.78) compared with the original SMR of 1.60 (95%CI: 1.31–1.93). The analysis did not deal with the exposure–response estimates.]

The mortality experience of crystalline silica sand workers in the United Kingdom was evaluated by Brown & Rushton (2005b). No overall excess of lung cancer was found (although there was a large, and highly significant, variation

in lung cancer SMRs between quarries; range: 0.27–1.61, both extremes $P < 0.01$. Relative risks rose with cumulative respirable crystalline silica dust exposure in the first two quartiles, but fell below 1.0 in the highest quartile, resulting in no trend being detected. [The Working Group noted that Steenland (2005) commented that the low exposures in the Brown & Rushton (2005b) study was likely to have impacted its power to detect a crystalline-silica effect.]

2.1.6 Other industries

Two studies having quantitative exposures to crystalline silica remain, although both industries are known to be associated with exposure to other known or suspected lung carcinogens. The first, by Watkins *et al.* (2002) was a small case–control study focused on asphalt fumes and crystalline silica exposure. Crystalline silica exposures were low compared to most other studies, and there were no significant lung cancer elevations or trends with exposure (Table 2.2 online). The second study was a nested case–control analysis of Chinese iron and steel workers (Xu *et al.*, 1996). A significant trend with cumulative total dust exposure was reported but not for cumulative crystalline silica dust exposure, although the relative risk for the highest crystalline silica-exposed group was elevated. The findings were adjusted for smoking, but not for benzo[*a*]pyrene exposures, for which the relative risks demonstrated a clear and significant trend with cumulative exposure level.

2.1.7 Semiquantitative exposure and expert-opinion studies

The studies that follow used quantitative exposure measurements in deriving crystalline silica exposure estimates for individuals but ultimately converted them to exposure scores or categories in the epidemiological analysis. Hessel *et al.* (1986) undertook a case–control study of lung cancer and cumulative crystalline silica exposure in South African gold miners after coding the dust measurements to four discrete levels (0, 3, 6, 12). No exposure–response was detected. Neither was any evidence of exposure–response detected in the later necropsy study of South African gold miners (Hessel *et al.*, 1990) that used the same approach to code the exposure data. [The Working Group noted that the study methods in the case–control study may have led to overmatching for exposure in the case–control study, and that there may have been some selection bias and exposure misclassification in the second study.]

de Klerk & Musk (1998) undertook a nested case–control analysis of lung cancer within a cohort study of gold miners and showed exposure–response for log of cumulative exposure (exposure-score–years) but not for any other index of exposure. The analysis adjusted for smoking, bronchitis, and nickel exposures, and took account of asbestos exposure. The study by Kauppinen *et al.* (2003) on road pavers found a relative risk for lung cancer of 2.26 in the highest exposure group, but there was no evidence of a linear trend of risk with level of exposure. No adjustment was made for concomitant exposures to PAHs, diesel exhaust, and asbestos, nor smoking. Moulin *et al.* (2000) conducted a nested case–control study to examine lung cancer among workers producing stainless steel and metallic alloys. Their results on 54 cases and 162 controls, adjusted for smoking but not for other confounders, indicated a marginally significant evidence of a trend with increasing crystalline silica exposure as well as with PAH exposure.

Two population-based studies that involved substantial expert opinion in assigning dust levels in developing quantitative crystalline silica exposures Brüske-Hohlfeld *et al.* (2000) and Pukkala *et al.* (2005) showed an increasing risk of lung cancer with increasing crystalline silica exposure after adjustment for smoking, and in the latter study, also for social class and exposure to asbestos.

2.1.8 Pooled analysis, meta-analyses, and other studies

Steenland *et al.* (2001) reported on a case–control analysis nested within a pooled study of data from ten cohorts from a variety of industries and countries (Table 2.2 online). It included information on diatomaceous, granite, industrial sand, and pottery workers, and workers in tungsten, tin, and gold mines. Results from all of the studies had been previously published, although not all had originally employed quantitative estimates of crystalline silica exposure; and for half, the duration of follow-up had been extended. All indices of cumulative crystalline silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends with lung cancer risk ($P < 0.0001$), and average exposure demonstrated a less significant trend ($P < 0.05$). Of these indices, log cumulative exposure led to homogeneity in findings across the cohorts ($P = 0.08$ and 0.34 for unlagged and 15-year lag respectively). Findings were similar for the mining and non-mining subgroups. No adjustment was made for smoking and other confounders, although it was noted that smoking had previously been shown not to be a major confounder in five of the ten studies. Analyses of subsets of the data omitting cohorts with suspected other confounders (radon in South African gold mines, and arsenic or PAHs in Chinese tin miners and pottery workers) did not change the overall findings. [The Working Group noted that the robustness in the findings to exclusion of cohorts with potential confounders from other occupational exposures indicates that any confounding in the individual studies were unlikely to have had an impact on their findings related to crystalline silica.]

The presence of silicosis in an individual is a biomarker of high exposure to crystalline silica dust. Accordingly, studies of individuals with silicosis have the potential to provide useful information on the lung cancer risk associated with exposure to crystalline silica. Three meta-analyses have focused on the risk of lung cancer among individuals with silicosis (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Lacasse *et al.*, 2005). Erren *et al.* (2009) also provide summary information in an electronic supplement to their article. Four others have looked at crystalline silica exposure (including silicosis status unknown and those without silicosis; Steenland & Stayner, 1997; Kurihara & Wada, 2004; Pelucchi *et al.*, 2006; Erren *et al.*, 2009). The number of studies included ranged from 11 in a meta-analysis focused on individuals without silicosis (Erren *et al.*, 2009) to 43 (Pelucchi *et al.*, 2006) in a study of those with and without silicosis. Reasons for this variation included: the publication date, the time period of interest, whether the study was focused on those with or without silicosis, the originating country of the studies, and analysis-specific criteria. For example, Steenland & Stayner (1997) rejected studies of miners and foundry workers on the assumption that they had the greatest potential for confounding exposures, and Smith *et al.* (1995) rejected certain studies they deemed under or overestimated the risk of lung cancer. Overall, of the total of 112 publications included by one or more of the seven meta-analyses, none were common to all analyses.

The detailed results from the seven meta-analyses are shown in Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.3.pdf. In brief, all analyses except for those devoted to categories without silicosis found an elevated lung cancer risk, whether occurring among those with silicosis or among crystalline-silica-exposed workers, or arising from cohort or case–control studies. [The Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of crystalline silica exposure, because individuals with the highest exposures tend to be omitted. Limiting the range of exposure results in reduced power to detect associations.] Overall, the rate ratios were

very similar across studies (1.74–2.76 for those with silicosis, and 1.25–1.32 for workers exposed to crystalline silica). Results from case–control studies, where there is greater opportunity to control for smoking, revealed lower rate ratios than from cohort studies in two analyses, greater rate ratios in two, and about the same in the fifth (the sixth analysis did not break the results out separately by study type). Moreover, the supplementary materials of Erren *et al.* (2009) show equal risk for crystalline silica exposure in unadjusted and smoking-adjusted studies. The two available analyses providing results on workers exposed to crystalline silica by type of study reported larger rate ratios from the case–control studies.

A further meta-analysis examined exposure–response (Lacasse *et al.*, 2009) rather than overall risk, and for this reason its findings are reported separately. The analysis included findings from ten studies having quantitative measurements of crystalline silica exposure and adjustment for smoking. An increasing risk of lung cancer was observed with increasing cumulative exposure to crystalline silica above a threshold of 1.84 mg/m^3 per year. Although the overall findings were heterogeneous, they were similar to those from a subset of seven more homogeneous studies.

Many of the meta-analyses noted that a lung cancer risk was apparent either after adjusting for smoking or among non-smokers (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Kurihara & Wada, 2004; Lacasse *et al.*, 2005). Yu & Tse (2007) further explored the issue of smoking on the interpretation of the published cohort and case–control studies of crystalline silica exposure and lung cancer. In this, they examined reported SMRs and standardized incidence ratios (SIR) for lung cancer reported in ten different published studies, and concluded that the risk had been systematically underreported for never smokers. After adjustment, five of the ten SMRs and SIRs showed significant lung cancer excesses among never smokers compared to two when unadjusted, and ranged from 2.60–11.93. The SMRs and SIRs for ever smokers were reduced after adjustment for smoking, but tended to retain their statistical significance.

2.2 Other cancers

2.2.1 Cancer of the stomach

In the 40 reports with information on cancer of the stomach, 18 had relative risks > 1.0 (including three significantly elevated), and 22 with relatives risks ≤ 1.0 (including two significantly reduced).

2.2.2 Digestive, gastro-intestinal, or intestinal cancers

In the 15 reports of digestive, gastro-intestinal, or intestinal cancer, seven had relative risks > 1.0 (including one significantly elevated), and eight with reltaive risks ≤ 1.0 (two significantly reduced).

2.2.3 Cancer of the oesophagus

In the 14 reports of oesophageal cancer, five had relative risks > 1.0 (including three significantly elevated), and nine with relative risks ≤ 1.0.

Wernli *et al.* (2006) reported a hazard ratio of 15.80 (95%CI: 3.5–70.6) among Chinese textile workers exposed for over 10 years to crystalline silica dust. In Chinese refractory brick workers, Pan *et al.* (1999) found not only a significant elevation with being ever exposed to crystalline silica dust (RR, 2.75; 95%CI: 1.44–5.25), but also a clear exposure–response relationship with years of exposure, adjusting for smoking and other personal factors. [The Working Group noted that confounding from exposure to PAHs could not be ruled out in the above two studies.]

Yu *et al.* (2007) reported an overall SMR for cancer of the oesophagus of 2.22 (95%CI: 1.36–3.43), and an SMR of 4.21 (95%CI: 1.81–8.30)

among caisson workers (who were noted to have had higher exposures to crystalline silica dust than non-caisson workers). The relative risk of oesophageal cancer for caisson workers with silicosis was reduced to 2.34 after adjusting for smoking and alcohol drinking. No excess risk of oesophageal cancer was observed among the non-caisson workers with silicosis after adjustment.

2.2.4 Cancer of the kidney

In the eight reports on cancer of the kidney, five had relative risks > 1.0 (including two significantly elevated), and three with relative risks ≤ 1.0. The two with significantly elevated risks provided information on exposure–response relationships with crystalline silica exposure, although neither formally evaluated this. In US sand and gravel workers (McDonald *et al.*, 2005), a non-significant negative trend with increasing crystalline silica exposure was observed. However, in Vermont granite workers (Attfield & Costello, 2004), kidney cancer SMRs increased almost monotonically with increasing exposure (except for the last exposure group), and the SMR of 3.12 in the penultimate exposure group was significantly elevated.

2.2.5 Others

There have been isolated reports of excesses in other cancers but the evidence is, in general, too sparse for evaluation. Elci *et al.* (2002) reported an excess of cancer of the larynx in workers potentially exposed to crystalline silica dust, particularly for supraglottic cancer (OR, 1.8; 95%CI: 1.3–2.3), with a significant exposure–response relationship.

2.3 Synthesis

Findings of relevance to lung cancer and crystalline silica exposure arise from five main industrial settings: ceramics, diatomaceous earth, ore mining, quarries, and sand and gravel. Of these, the industries with the least potential for confounding are sand and gravel operations, quarries, and diatomaceous earth facilities. Among those industry segments, most studies with quantitative exposures report associations between crystalline silica exposure and lung cancer risk. The findings are supported by studies in these industries that lack quantitative exposures. Results from the other industry segments generally added support although some studies had potential confounding from arsenic, radon, or PAHs. In one case among Chinese tin miners, the arsenic and crystalline silica exposures were virtually collinear, and no adjustment could be made for arsenic. In another (Chinese pottery workers), adjustment for PAHs removed a significant crystalline silica exposure effect, and in a third, among iron and copper miners, the crystalline silica effect disappeared after adjustment for radon. In these, the role of crystalline silica exposure must be regarded as unclear. Mixed findings were reported among gold, tungsten, and lead/zinc miners.

The strongest evidence supporting the carcinogenicity of crystalline silica in the lung comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure–response, while all of the meta-analyses strongly confirmed an overall effect of crystalline silica dust exposure despite their reliance on different studies in coming to their conclusions.

Cancers other than that of the lung have not been as thoroughly researched. In many cases the findings were reported in passing, in analyses focused on lung cancer, and rarely have the data examined exposure–response with crystalline silica exposure or its surrogates.

3. Cancer in Experimental Animals

No additional relevant cancer bioassays have been conducted since the previous *IARC Monograph* (IARC, 1997) except for a study in hamsters by inhalation (Muhle *et al.*, 1998), and a study in mice by intratracheal instillation (Ishihara *et al.*, 2002). Studies from the previous evaluation considered adequate are summarized below together with the new studies published since.

3.1 Inhalation exposure

See Table 3.1

3.1.1 Mouse

Female BALB/cBYJ mice exposed to crystalline silica by inhalation (Wilson *et al.*, 1986) did not have an increase in lung tumours compared to controls. Pulmonary adenomas were observed in both the silica-exposed (9/60) and the control animals (7/59). [The Working Group noted that the study groups were small (6–16 mice).]

3.1.2 Rat

Male and female F344 rats were exposed to 0 or 52 mg/m^3 of crystalline silica (Min-U-Sil) over a 24-month period. Interim removals of ten males and ten females per group were made after 4, 8, 12, and 16 months of exposure. Half of those removed were necropsied, and half were held until the end of the 24 months. None of the controls developed a lung tumour. In the silica-exposed rats, the first pulmonary tumour appeared at 494 days, and the incidence was 10/53 in females and 1/47 in males (Dagle *et al.*, 1986).

One group of 62 female F344 rats was exposed by nose-only inhalation to 12 mg/m^3 crystalline silica (Min-U-Sil) for 83 weeks. An equal number of controls was sham-exposed to filtered air, and 15 rats were left untreated. The animals were observed for the duration of their lifespan. There were no lung tumours in the sham-exposed group, and 1/15 unexposed rats had an adenoma of the lung. In the quartz-exposed rats, the incidence of lung tumours was 18/60 (Holland *et al.*, 1983, 1986; Johnson *et al.*, 1987).

Groups of 50 male and 50 female viral antibody-free SPF F344 rats were exposed by inhalation to 0 or 1 mg/m^3 silica (DQ12; 87% crystallinity as quartz) for 24 months. The rats were then held for another 6 weeks without exposure. The incidence of lung tumours in the silica-exposed rats was 7/50 males and 12/50 in females. Only 3/100 controls had lung tumours (Muhle *et al.*, 1989, 1991, 1995).

Three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by nose-only inhalation to 6.1 or 30.6 mg/m^3 DQ12 quartz for 29 days. Interim sacrifices were made immediately after the exposure and at 6, 12, and 24 months, with the final sacrifice at 34 months after exposure. The total animals with lung tumours was 0 (controls), 37/82 (low dose), and 43/82 (high dose). Many animals had multiple tumours (Spiethoff *et al.*, 1992).

3.1.3 Hamster

Groups of 50 male and 50 female Syrian golden hamsters were exposed to 0 (control) or 3 mg/m^3 DQ12 quartz (mass median aerodynamic diameter, 1.3 µm) for 18 months. The experiment was terminated 5 months later. In the silica-exposed group, 91% of the animals developed very slight to slight fibrosis in the lung, but no significant increase of lung tumours was observed (Muhle *et al.*, 1998)

Table 3.1 Studies of cancer in experimental animals exposed to crystalline silica (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size, GSD	Incidence of tumours in respiratory tract	Significance	Comments
Mouse, BALB/c BYJ (F) 150, 300 or 570 d Wilson *et al.* (1986)	0, 1.5, 1.8 or 2.0 mg/m^3 8 h/d, 5 d/wk 6–16 animals Diameter < 2.1 µm	Lung (adenomas): 7/59 (control), 9/60 (all exposed)	[NS]	
Rat, F344 (M, F) 24 mo Dagle *et al.* (1986)	0, 52 mg/m^3 6 h/d, 5 d/wk 72/sex MMAD, 1.7–2.5 µm; GSD, 1.9–2.1	Lung (epidermoid carcinomas): M–0/42 (control), 1/47 F–0/47 (control), 10/53	[NS] [$P < 0.002$]	
Rat, F344 (F) Lifespan Holland *et al.* (1983, 1986); Johnson *et al.* (1987)	0, 12 mg/m^3 6 h/d, 5 d/wk for 83 wk 62 animals MMAD, 2.24 µm; GSD, 1.75	Lung (tumours): 0/54 (control), 18/60 (11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas)	[$P < 0.001$]	Nose-only inhalation exposure. Age unspecified
Rat, SPF F344 (M, F) 30 mo Muhle *et al.* (1989, 1991, 1995)	0, 1 mg/m^3 6 h/d, 5 d/wk for 24 mo 50/sex MMAD, 1.3 µm; GSD, 1.8	Lung (tumours): 3/100 (control M, F), 7/50 (M), 12/50 (F) M–1 adenoma, 3 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours, 1 adenosquamous carcinoma, 1 squamous cell carcinoma F–2 adenomas, 8 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours	Unspecified (M) [$P < 0.05$] (F)	
Rat, Wistar (F) Up to 35 mo Spiethoff *et al.* (1992)	0, 6.1, 30.6 mg/m^3 6 h/d, 5 d/wk for 29 d 90 animals MMAD, 1.8 µm; GSD, 2.0	0/85 (control), 37/82 (low dose), 43/82 (high dose) Multiple tumours/rat: 21 bronchiolo-alveolar adenomas, 43 bronchiolo-alveolar carcinomas, 67 squamous cell carcinomas, 1 anaplastic carcinoma	[$P < 0.0001$] (both doses)	Nose-only inhalation exposure

d, day or days; F, female; GSD, geometric standard deviation; h, hour or hours; M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NS, not significant; wk, week or weeks

3.2 Intranasal administration

3.2.1 Mouse

Two groups of 40 female (C57xBALB/c) F_1 mice received a single intranasal instillation of 4 mg of synthetic *d*- or *l*-quartz. A group of 60 females received an intranasal instillation of saline. Survivors were killed at 18 months after treatment, and the incidence of lymphomas and leukaemias combined was 0/60 (controls), 2/40 (*d*-quartz), and 6/40 (*l*-quartz) (Ebbesen, 1991). [The Working Group noted that the study was not designed to detect silica-induced lung tumours, and also noted the lack of information on quartz retention.]

3.3 Intratracheal administration

See Table 3.2

3.3.1 Mouse

A group of 30 male A/J mice, 11–13 weeks old, received weekly intratracheal instillations of 2.9 mg quartz for 15 weeks. A group of 20 mice received instillations of vehicle [unspecified]. Animals were killed 20 weeks after the instillations. The incidences of lung adenomas were 9/29 in the controls, and 4/20 for the silica-instilled mice, values that were not statistically different (McNeill *et al.*, 1990).

Ishihara *et al.* (2002) administered a single dose (2 mg in saline/mouse) of crystalline silica to a group of four C57BL/6N mice by intratracheal instillation to study subsequent genotoxic effects. A control group of four animals was instilled saline only. Silicotic lesions were observed in the lungs of the exposed mice, but no pulmonary neoplasms were observed after 15 months.

3.3.2 Rat

A group of 40 Sprague Dawley rats [sex unspecified] received weekly instillations of 7 mg quartz (Min-U-Sil) in saline for 10 weeks. Another groups of 40 rats received instillations of saline alone, and 20 rats remained untreated. Animals were observed over their lifespan. The incidence of lung tumours in quartz-treated rats was 6/36, 0/40 in the saline controls, and 0/18 in the untreated rats (Holland *et al.*, 1983).

Groups of 85 male F344 rats received a single intratracheal instillation of 20 mg quartz in deionized water, Min-U-Sil or novaculite, into the left lung. Controls were instilled with vehicle only. Interim sacrifices of ten rats were made at 6, 12, and 18 months with a final sacrifice at 22 months. The incidence of lung tumours in the Min-U-Sil-instilled rats was 30/67, in the novaculite-treated rats 21/72, and in controls 1/75. All of the lung tumours were adenocarcinomas, except for one epidermoid carcinoma in the novaculite-treated rats (Groth *et al.*, 1986).

Groups of male and female F344/NCr rats [initial number unspecified] received one intratracheal instillation of 12 or 20 mg quartz in saline or 20 mg of ferric oxide (non-fibrogenic dust) in saline. Interim sacrifices were made at 11 and 17 months with a final sacrifice at 26 months. There was a group of untreated controls observed at unscheduled deaths after 17 months. No lung tumours were observed in the ferric-oxide-treated rats and only one adenoma was observed in the untreated controls. The high incidences of benign and mainly malignant lung tumours observed in the quartz-treated rats is summarized in Table 3.3 (Saffiotti, 1990, 1992; Saffiotti *et al.*, 1996).

Six groups of 37–50 female Wistar rats, 15 weeks old, received either a single or 15 weekly intratracheal instillation of one of three types of quartz preparations in saline (see Table 3.4). A control group received 15 weekly instillations of saline. To retard the development of silicosis,

Table 3.2 Studies of cancer in experimental animals exposed to silica (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size	Incidence of tumours	Significance
Mouse, A/J (M) 20 wk McNeill *et al.* (1990)	0, 2.9 mg Weekly for 15 wk 30, 20 (controls) 1–5 µm (size not further specified)	Lung (adenomas): 9/29 (control), 4/20 Tumour multiplicity: 0.31 ± 0.09 (control), 0.20 ± 0.09	[NS] [NS]
Rat, Sprague Dawley (NR) Lifespan Holland *et al.* (1983)	0 (saline), 7 mg Weekly for 10 wk 40 animals 1.71 ± 1.86 µm	Lung (1 adenoma, 5 carcinomas): 0/40 (control), 6/36	[P<0.05] (carcinomas)
Rat, F344 (M) 22 mo Groth *et al.* (1986)	0, 20 mg once only 85 animals < 5 µm	Lung (adenocarcinomas): 1/75 (control), 30/67	[P<0.001]
Rat, F344/NCr (M, F) 11, 17 or 26 mo Saffiotti (1990, 1992); Saffiotti *et al.* (1996)	0, 12, 20 mg quartz Once only Ferric oxide (20 mg) was negative control [Initial number of rats, NR] 0.5–2.0 µm	High incidences of benign and mainly malignant lung tumours in quartz-treated rats reported in Table 3.3 No tumours observed in ferric oxide group One adenoma in untreated controls	NR
Rat, Wistar Lifespan Pott *et al.* (1994)	0 (saline), one single or 15 weekly injections of one of 3 types of quartz Some rats received PVNO to protect against silicosis 37–50/group	Incidences of benign and malignant lung tumours in quartz-treated rats are shown in Table 3.4 No tumours observed in saline-treated rats	NR
Hamster Syrian Golden (NR) Lifespan Holland *et al.* (1983)	0 (saline), 3, 7 mg quartz (Min-U-Sil) Once a wk for 10 wk 48/group; 68 (controls) 1.71 ± 1.86 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) Lifespan Renne *et al.* (1985)	0 (saline), 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) weekly for 15 wk 25–27/group MMAD, 5.1 µm Geometric diameter, 1.0 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) 92 wk Niemeier *et al.* (1986)	0 (saline), 1.1 (Sil-Co-Sil) or 0.7 (Min-U-Sil) mg One group received 3 mg ferric oxide 50/group 5 µm (Min-U-Sil)	No tumours in saline controls or in Sil-Co-Sil groups 1 adenosquamous carcinoma of the bronchi and lung in Min-U-Sil group and 1 benign tumour of the larynx in ferric oxide group	

M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NR, not reported; NS, not significant; PVNO, polyvinylpyridine-*N*-oxide; wk, week or weeks

Table 3.3 Incidence, numbers, and histological types of lung tumours in F344/NCr rats after a single intratracheal instillation of quartz

Treatment		Observation time	Lung tumours	
Material	Dose[a]		Incidence	Types
Males				
Untreated	None	17–26 mo	0/32	
Ferric oxide	20 mg	11–26 mo	0/15	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo	3/18 (17%)	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo	6/19 (32%)	
		17–26 mo	12/14 (86%)	
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo	2/18 (11%)	5 adenomas, 14 adenocarcinomas, 1 mixed carcinoma
		Killed at 17 mo	7/19 (37%)	
		17–26 mo	7/9 (78%)	
Females				
Untreated	None	17–26 mo	1/20 (5%)	1 adenoma
Ferric oxide	20 mg	11–26 mo	0/18	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo	8/19 (42%)	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo	10/17 (59%)	
		17–26 mo	8/9 (89%)	
	20 mg	17–26 mo	6/8 (75%)	1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, 1 epidermoid carcinoma
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo	7/18 (39%)	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, 5 epidermoid carcinomas
		Killed at 17 mo	13/16 (81%)	
		17–26 mo	8/8 (100%)	

[a] Suspended in 0.3 or 0.5 mL saline

HF, hydrogen fluoride; mo, month or months

From Saffiotti (1990, 1992), Saffiotti *et al.* (1996)

Table 3.4 Incidence, numbers, and histological types of lung tumours in female Wistar rats after intratracheal instillation of quartz

Material	Surface area	No. of instillations	No. of rats examined	No. and #% of rats with primary epithelial lung tumours[a]					Other tumours[b]
	(m^2/g)	(del # × mg)		Adenoma	Adenocarcinoma	Benign CKSCT	Squamous cell carcinoma	Total (%)	
Quartz (DQ 12)	9.4	15 × 3	37	0	1z	11	1 + 1y	38	1
Quartz (DQ 12) + PVNO	9.4	15 × 3	38	0	1 + 3z	8 + 1x	4+1x+3y+1z	58	2
Quartz (DQ 12)	9.4	1 × 45	40	0	1	7	1	23	2
Quartz (Min-U-Sil)	–	15 × 3	39	1	4 + 4z	6	1+2y+2z+1y,z	54	3
Quartz (Min-U-Sil) + PVNO	–	15 × 3	35	1	2 + 1x	8	5+1x+1y+1z	57	3
Quartz Sykron (F 600)	3.7	15 × 3	40	0	3	5	3 + 1z	30	1
0.9% Sodium chloride	–	15 × 0.4 mL	39	0	0	0	0	0	5

[a] If an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows:[x]adenoma; [y]adenocarcinoma; [z]benign CKSCT.

[b] Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

PVNO, polyvinylpyridine-*N*-oxide; CKSCT, cystic keratinizing squamous cell tumour

From Pott *et al.* (1994)

two of the groups received injections of polyvinylpyridine-*N*-oxide. All groups of quartz-exposed rats had a significant increase in lung tumours, and the rats protected against silicosis developed more pulmonary squamous cell carcinomas than rats that were not protected (Pott *et al.*, 1994).

3.3.3 Hamster

Two groups of 48 Syrian hamsters [sex unspecified] received intratracheal instillations of 3 or 7 mg quartz (Min-U-Sil) in saline once a week for 10 weeks. A group of 68 hamsters received saline alone, and another group of 72 hamsters were untreated. All animals were observed for their lifespan. No lung tumours were observed in any of the groups (Holland *et al.*, 1983).

Groups of 25–27 male Syrian golden hamsters, 11–weeks old, received weekly intratracheal instillation of 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) in saline for 15 weeks. Groups of 27 saline-instilled hamsters and 25 untreated controls were used as controls. Animals were observed for their lifespan. No lung tumours were observed in any group (Renne *et al.*, 1985).

Three groups of 50 male Syrian golden hamsters received weekly instillations of 1.1 mg of quartz as Sil-Co-Sil, or 0.7 mg of quartz as Min-U-Sil, or 3 mg of ferric oxide (non-fibrogenic particle) in saline for 15 weeks. A group of 50 saline-instilled hamsters served as controls. Survivors were killed at 92 weeks after the beginning of the instillations. No respiratory tract tumours were observed in the hamsters exposed to Sil-Co-Sil or in the saline controls. One adenosquamous carcinoma of the bronchi and lung was observed in the Min-U-Sil group, and one benign tumour of the larynx in the ferric-oxide-exposed group (Niemeier *et al.*, 1986).

3.4 Intrapleural and intrathoracic administration

3.4.1 Mouse

One mouse study was reported in the previous *IARC Monograph* (IARC, 1997) in which the route of exposure was via a single intrathoracic injection of tridymite. The study was only reported as an abstract, and therefore is not described here (Bryson *et al.*, 1974).

3.4.2 Rat

Two groups of 48 male and 48 female standard Wistar rats and two groups 48 male and 48 female SPF Wistar rats were given a single intrapleural injection of 20 mg alkaline-washed quartz (size, < 5 µm) in saline, and observed for their lifespan. Control rats received injections of 0.4 mL saline alone. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in 39/95 quartz-treated SPF rats [$P < 0.001$] (23 histiocytic lymphomas, five Letterer-Siwe/Hand-Schüller-Christian disease-like tumours, one lymphocytic lymphoma, four lymphoblastic lymphosarcomas, and six spindle cell sarcomas), and in 31/94 quartz-treated standard rats [$P < 0.001$] (30 histiocytic lymphomas and one spindle-cell sarcoma). In the SPF control animals, 8/96 rats had tumours (three lymphoblastic lymphosarcomas, five reticulum cell sarcomas), 7/85 standard rat controls had tumours (one lymphoblastic lymphosarcoma, and six reticulum cell sarcomas) (Wagner & Berry, 1969; Wagner, 1970; Wagner & Wagner, 1972). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

In a second study, with the same dosing regimen and type of quartz, 23 rats developed malignant reticuloendothelial system tumours (21 malignant lymphomas of the histiocytic type [MLHT], two thymomas, and one lymphosarcoma/thymoma/spindle cell sarcoma) in 80 male

and 80 female SPF Wistar rats after 120 weeks. In another experiment, 16 male and 16 female SPF Wistar rats dosed similarly with Min-U-Sil quartz were observed until they were moribund. Eight of the 32 rats developed MLHT and three developed thymomas/lymphosarcomas. In a last experiment with the same experimental design, 18 of 32 SPF Wistar rats that had been injected with cristobalite developed malignant lymphomas (13 MLHT and five thymomas/lymphosarcomas). No MLHT and one thymoma/lymphosarcoma tumours were observed in 15 saline-injected control rats. (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified, and that no statistics were provided.]

In one experiment, groups of 16 male and 16 female Wistar rats were given intrapleural injections of 20 mg of four types of quartz (Min-U-Sil, D&D, Snowit, and DQ12). The animals were observed for their lifespan. For all but the group treated with DQ12 quartz, there was a statistically significant increase in MLHT over saline controls (Table 3.5). In a second experiment with the same experimental design, two other strains of rats were injected Min-U-Sil (12 male and 12 female PVG rats and 20 male and 20 female Agus rats). A non-significant increase in MLHT was observed in both strains, and there was no MLHT in the saline controls. In a third experiment with the same experimental design, cristobalite was injected, and 4/32 treated Wistar rats developed MLHT [not significant], but none of the 32 saline controls did. In a final experiment, 16 male and 16 female Wistar rats were injected triolymite (size, < 0.5 μm; 0.35×10^6 particle/μg), and observed for their lifespan. A total of 16/32 Wistar rats developed MLHT, whereas no such tumours were observed in the 32 saline controls (Wagner *et al.*, 1980). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

Two groups of 36 2-month-old male Sprague-Dawley rats, received a single intrapleural injection of 20 mg DQ12 quartz in saline or saline alone, and were observed for their lifespan. Twenty-seven male rats served as untreated controls. Six malignant histiocytic lymphomas and two malignant Schwannomas were observed in the quartz-treated group [not significant], and one chronic lymphoid leukaemia and one fibrosarcoma were observed in the saline group and untreated controls, respectively (Jaurand *et al.*, 1987).

3.5 Intraperitoneal administration

3.5.1 Rat

Two groups of 16 male and 16 female SPF Wistar rats received a single intraperitoneal injection of 20 mg of Min-U-Sil quartz in saline, and were observed for their lifespan. There were 12 saline controls [sex unspecified]. A total of 9/64 quartz-exposed rats developed malignant lymphomas (two MLHT and seven thymoma/lymphosarcomas). None of the saline controls developed MLHT, but one thymoma/lymphosarcoma was noted (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

3.6 Subcutaneous administration

3.6.1 Mouse

Two groups of 40 female (C57xBALB/c) F_1 mice received a single subcutaneous injection of 4 mg of *d*- or *l*-quartz. A group of 60 female mice served as saline controls. At 18 months after injection, there was an incidence of lymphomas/leukemias of 0/60, 1/40 and 12/40 ($P < 0.001$), and of liver adenomas of 0/60, 1/40 and 3/40 for the saline controls, *d*-quartz and *l*-quartz groups, respectively. No injection-site tumours were reported (Ebbesen, 1991).

Table 3.5 Incidences of malignant lymphoma of the histiocytic type (MLHT) in Wistar rats after an intrapleural injection of 20 mg quartz/animal

Sample	No. of particles × 10^6/µg	Size distribution (%)			Mean survival (days)	Incidence of MLHT (%)[a]
		< 1 µm	1–2 µm	2–4.6 µm		
Min-U-Sil (a commercially prepared crystalline quartz probably 93% pure)	0.59	61.4	27.9	9.1	545	11/32 (34%)b
D&D (obtained from Dowson & Dobson, Johannesburg, pure crystalline quartz)	0.30	48.4	33.2	18.4	633	8/32 (25%)b
Snowit (commercially prepared washed crystals)	1.1	81.2	12.9	5.6	653	8/32 (25%)b
DQ12 (standard pure quartz)	5.0	91.4	7.8	0.8	633	5/32 (16%)
Saline controls	–	–	–	–	717	0 [0/32] (0%)

[a] Sex unspecified
[b] [Significantly different from controls by Fisher Exact test, $P < 0.05$]
From Wagner *et al.* (1980)

3.7 Intravenous administration

3.7.1 Mouse

Groups of 25 male and 25 female strain A mice were injected in the tail vein with 1 mg quartz in 0.1 mL of saline, with a control group of 75 male and female untreated animals. Animals were killed 3, 4.5 or 6 months after injection. There was no difference in the incidences and multiplicities of pulmonary adenomas between treated and untreated animals (Shimkin & Leiter, 1940).

3.8 Administration with known carcinogens

3.8.1 Inhalation

(a) Rat

Studies have been completed to determine the effect of co-exposure to silica and Thorotrast, a known carcinogen (See Table 3.6). Two sets of three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by inhalation to 0, 6, or 31 mg/m^3 of DQ12 quartz (mass median diameter, 1.8 µm; GSD, 2.0) for 6 hours/day 5 days/week for 29 days. One week after the inhalation exposure, one group of quartz-exposed rats and one group of sham-exposed rats received an intravenous injection of Thorotrast (2960 Bq ^{228}Th/mL, 0.6 mL). Controls were only sham-exposed. In each of the six groups, interim sacrifices of three or six animals each were made 0, 6, 12 and 24 months after the end of exposure. The experiment was terminated 34 months after the end of exposure. In rats that were exposed to silica by inhalation and then given Thorotrast, there was a small increase in lung tumours compared to the already high incidence of benign and malignant tumours induced by silica alone (Spiethoff *et al.*, 1992).

3.8.2 Intratracheal administration

(a) Rat

Four groups of white rats (group sizes varied from 28 to 70, with approximately equal numbers of males and females) were given either no treatment or a single instillation of 5 mg benzo[*a*]pyrene or an instillation of 50 mg quartz (size, 82% < 2 µm) and 5 mg benzo[*a*]pyrene (Group A) or 50 mg quartz and a later (1 month) instillation of 5 mg benzo[*a*]pyrene (Group B). The rats were observed until death. There were no

Table 3.6 Incidence, numbers and histological types of lung tumours in female Wistar rats after inhalation exposure to quartz and/or Thorotrast

Treatment	Number of rats[a]	Lung tumours				
		Incidence	Total number	Histological type		
		Observed		Bronchiolo-alveolar adenoma	Bronchiolo-alveolar carcinoma	Squamous cell carcinoma
Controls	85	–	–	–	–	–
Low-dose quartz	82	37	62	8	17	37
High-dose quartz	82	43	69	13	26	30
Thorotrast (Tho)	87	3	6	–	5	1
Low-dose quartz + Tho	87	39	68	10	28	30
High-dose quartz + Tho	87	57	98	16	47	35

[a] Without the animals sacrificed 0 and 6 months after the end of inhalation exposure.
From Spiethoff *et al.* (1992)

lung tumours in the untreated rats (0/45), nor in those exposed to benzo[*a*]pyrene alone (0/19). In the combined exposures to benzo[*a*]pyrene and quartz, an increased incidence in lung tumours was observed (Group A, 14/31, 11 squamous cell carcinomas and three papillomas; Group B, 4/18, two papillomas and two carcinomas) (Pylev, 1980). [The Working Group noted the absence of a group exposed to quartz alone.]

(b) Hamster

Groups of 50 male Syrian golden hamsters received weekly intratracheal instillations for 15 weeks in saline of 3 mg benzo[*a*]pyrene or 3 mg ferric oxide or 3 mg ferric oxide plus 3 mg benzo[*a*]pyrene or 1.1 mg Sil-Co-Sil or 1.1 mg Sil-Co-Sil plus 3 mg benzo[*a*]pyrene or 0.7 mg Min-U-Sil or 0.7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene or 7 mg Min-U-Sil or 7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene. Fifty male controls received saline alone. Survivors were killed at 92 weeks after exposure. Co-exposures with silica caused an enhancement of the number of respiratory tract tumours induced by benzo[*a*]pyrene (mainly in the bronchus and lung) (Niemeier *et al.*, 1986; Table 3.7).

3.9 Synthesis

Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters. Rats are known to be more sensitive than are mice or hamsters to the induction of lung tumours due to other inhaled poorly soluble particles, such as carbon black (Mauderly *et al.*, 1994).

Quartz-induced lymphoma incidence was also increased in several experiments in rats after intrapleural administration, and in one study in mice after subcutaneous administration. Tridymite- and cristobalite-induced lymphomas were observed in only a single experiment.

Table 3.7 Incidences of respiratory tract tumours in Syrian golden hamsters after intratracheal administration of quartz with or without benzo[*a*]pyrene

Treatment	No. of animals	No. of animals with respiratory tract tumours	No. of respiratory tract tumours[a] by site			Mean latency (wk)
			Larynx	Trachea	Bronchus and lung	
Saline control	48	0	0	0	0	–
BaP	47	22	5	3	32	72.6
Ferric oxide	50	1	1	0	0	62
Ferric oxide + BaP	48	35b,c	5	6	69	70.2
Sil-Co-Sil	50	0	0	0	0	–
Sil-Co-Sil + BaP	50	36b,c	13	13	72	66.5
Min-U-Sil	50	1	0	0	1	68
Min-U-Sil + BaP	50	44b,c	10	2	111	68.5
Min-U-Sil + ferric oxide	49	0	0	0	0	–
Min-U-Sil + ferric oxide + BaP	50	38b,c	10	4	81	66.7

[a] Types of tumours: polyps, adenomas, carcinomas, squamous cell carcinomas, adenosquamous carcinomas, adenocarcinomas, sarcomas.
[b] Statistically significantly higher ($P < 0.00001$; two-tailed Fisher Exact test) compared with the corresponding group not treated with BaP.
[c] Statistically significantly higher ($P < 0.01$; two-tailed Fisher Exact test) compared with the BaP group.
BaP, benzo[*a*]pyrene
From Niemeier *et al.* (1986)

4. Other Relevant Data

4.1 Deposition and biopersistence

The inhalation of crystalline silica is associated with various lung diseases including acute silicosis or lipoproteinosis, chronic nodular silicosis, and lung cancer. Exposure to silica dust may also cause renal and autoimmune diseases (Steenland & Goldsmith, 1995; Stratta *et al.*, 2001; Cooper *et al.*, 2002; Otsuki *et al.*, 2007). In silicotic patients, alveolar macrophages collected by pulmonary lavage contain crystalline silica and at autopsy, elevated levels of quartz are found in the lungs and lymph nodes. Crystalline silica is poorly soluble and biopersistent; even after cessation of exposure, silicosis can progress and is a risk factor for the development of lung cancer (IARC, 1997).

Alveolar macrophages play a key role in silica-related toxicity, and therefore the cytotoxic potency of silica particles determine the degree of silica-related pathogenicity (IARC, 1997; Donaldson & Borm, 1998). The stronger the cytotoxicity of crystalline silica to alveolar macrophages, the higher the intensity of the inflammatory reaction, and the longer the residence time of the particle in the lung (Donaldson & Borm, 1998; Fenoglio *et al.*, 2000a).

Rodent inhalation studies have investigated the relationship between intrinsic particle toxicity, persistent inflammation, altered macrophage-mediated clearance, and biopersistence in the lung (Warheit *et al.*, 2007). Crystalline silica particles induce lung inflammation that persists even after cessation of exposure, with alveolar macrophages having reduced chemotactic responses and phagocytosis. Crystalline silica impairs macrophage-mediated clearance secondary to its cytotoxicity that allows these particles to accumulate and persist in the lungs (IARC, 1997). In humans, it is possible that co-exposure to tobacco smoke and crystalline silica may impair the clearance of these toxic particles (IARC, 2004).

4.2 Mechanisms of carcinogenicity

It is generally accepted that alveolar macrophages and neutrophils play a central role in diseases associated with exposure to crystalline silica (Hamilton *et al.*, 2008). An inflammation-based mechanism as described in IARC (1997) is a likely mechanism responsible for the induction of lung cancer associated with exposure to crystalline silica, although reactive oxygen species can be directly generated by crystalline silica polymorphs themselves, and can be taken up by epithelial cells. For this reason, a direct effect on lung epithelial cells cannot be excluded (Schins, 2002; Fubini & Hubbard, 2003; Knaapen *et al.* 2004).

4.2.1 Physicochemical features of crystalline silica dusts associated with carcinogenicity

The major forms or polymorphs of crystalline silica are the natural minerals quartz, tridymite, cristobalite, coesite, stishovite, and the artifical silica-based zeolites (porosils) (Fenoglio *et al.*, 2000a). Humans have been exposed only to quartz, tridymite, cristobalite, the other forms being very rare. Several amorphous forms of silica exist, some of which were classified in Group 3 (*not classifiable as to their carcinogenicity*) in the previous *IARC Monograph* (IARC, 1997). Also, it has been shown that this cytotoxicity is lowered with lowering hydrophilicity (Fubini *et al.*, 1999), which depends upon the circumstances under which the surface was created. For example, silica in fly ashes or volcanic dusts is generated at high temperatures, and is mostly hydrophobic.

The classification in Group 1 (*carcinogenic to humans*) of some silica polymorphs in the previous *IARC Monograph* (IARC, 1997) was preceded by a preamble indicating that crystalline silica did not show the same carcinogenic potency in all circumstances. Physicochemical features – polymorph characteristics, associated contaminants – may account for the differences found in humans and in experimental studies. Several studies on a large variety of silica samples, aiming to clarify the so-called "variability of quartz hazard" have indicated features and contaminants that modulate the biological responses to silica as well as several surface characteristics that contribute to the carcinogenicity of a crystalline silica particle (Donaldson & Borm, 1998; Fubini, 1998a; Elias *et al.*, 2000; Donaldson *et al.*, 2001). The larger potency of freshly ground dusts (e.g. as in sandblasting) has been confirmed in several studies; Vallyathan *et al.*, 1995), as immediately after cleavage, a large number of surface-active radicals are formed that rapidly decay (Damm & Peukert, 2009). The association with clay or other aluminium-containing compounds inhibits most adverse effects (Duffin *et al.*, 2001; Schins *et al.*, 2002a), iron in traces may enhance the effects but an iron coverage inhibits cytotoxicity and cell transformation (Fubini *et al.*, 2001). One study on a large variety of commercial quartz dusts has shown a spectrum of variability in oxidative stress and inflammogenicity *in vitro* and *in vivo*, which exceeds the differences previously found among different polymorphs (Bruch *et al.*, 2004; Cakmak *et al.*, 2004; Fubini *et al.*, 2004; Seiler *et al.*, 2004). Subtle differences in the level of contaminants appear to determine such variability. New studies *in vitro* and *in vivo* on synthesized nanoparticles of quartz (Warheit *et al.*, 2007) indicate a variability of effects also at the nanoscale. These new data clearly show that more or less pathogenic materials are comprised under the term "crystalline silica dusts." However, most studies, so far, have failed to identify strict criteria to distinguish between potentially more or less hazardous forms of crystalline silica.

The pathogenic potential of quartz seems to be related to its surface properties, and the surface properties may vary depending on the origin of the quartz. The large variability in silica hazard even within quartz particles of the same polymorph may originate from the

grinding procedure, the particle shape, the thermal treatment (determines the hydrophilicity of the particle), and the metal impurities (e.g. aluminium, iron) (Fubini *et al.*, 2004).

The toxicity of silica dust from various sources may be related either to the kind of silica polymorph or to impurities.

The correlation between artificially pure crystalline silicas (porosils) with similar physicochemical properties, but different micromorphology, size and surface area, was investigated (Fenoglio *et al.*, 2000a). Surface area and aspect ratio (elongated crystals with a higher aspect ratio than more isometric crystals) of the particulates tested in a cellular system (mouse monocyte-macrophage tumour cell line) correlate best with inhibition of cell proliferation after 24–72 hours experimental time. From the natural crystalline silicas, only stishovite did not show a cytotoxic effect; all the other natural polymorphs were rather toxic. Stishovite is made up of smooth round particles (Cerrato *et al.*, 1995) whereas quartz, tridymite, and cristobalite consist of particles with very sharp edges caused by grinding (Fubini, 1998a; Fubini *et al.*, 1990, 1999). Stishovite, the only polymorph with silicon in octahedral coordination, has densely packed hydroxyl-silanols on its surface that interact with hydrogen bonds with each other; for this reason, the interaction of silanols with cell membranes, which normally does occur, is dramatically reduced (Cerrato *et al.*, 1995).

Pure silica-zeolites with different particle forms exhibit similar cytotoxicity *in vitro* if compared at equal surface area instead of equal mass. The extent of free radical generation did not show a significant correlation with cytotoxicity in this short-term in-vitro test (Fenoglio *et al.*, 2000a). Free radicals generated by the particle may play a role in later stages of toxicity related to crystalline silica (Ziemann *et al.*, 2009). Both silicon-based surface radicals and iron ions located at the particle surface may be active centres for free radical release in solution (Fubini *et al.*, 2001).

As has already been demonstrated with quartz and cristobalite (Brown & Donaldson, 1996; Bégin *et al.*, 1987), the cytotoxicity of artificially pure silica-zeolites can be decreased by aluminium ions adsorbed onto the particle surface (Fenoglio *et al.*, 2000a). Crystalline silica may occur naturally embedded in clays or may be mixed with other materials in some commercial products. It is possible that these materials may adsorb onto the silica surface, and modify its reactivity. However, the extent of surface coverage and the potency of these modified crystalline silica particles after long-term residence in the lungs have not been systematically assessed.

A quartz sample isolated from bentonite clay obtained from a 100 to 112 million-year-old formation in Wyoming, USA, exhibits a low degree of internal crystal organization, and the surface of this quartz particles are occluded by coatings of the clay. This "quartz isolate" was compared in respect to its toxic potency after intratracheal instillation in rats with the quartz sample DQ12. The "quartz isolate" showed a much lower toxicity than DQ12 quartz, in agreement with the much lower surface reactivity of "quartz isolate" compared to the DQ12 quartz (Creutzenberg *et al.*, 2008; Miles *et al.*, 2008).

4.2.2 Direct genotoxicity and cell transformation

Reactive oxygen species are generated not only at the particle surface of crystalline silica, but also by phagocytic and epithelial cells exposed to quartz particles (Castranova *et al.*, 1991; Deshpande *et al.*, 2002). Oxidants generated by silica particles and by the respiratory burst of silica-activated phagocytic cells may cause cellular and lung injury, including DNA damage. Lung injury may be initiated and amplified by severe inflammation (Donaldson *et al.*, 2001; Castranova, 2004; Knaapen *et al.*, 2004). Various

products (chemotactic factors, cytokines, growth factors) released by activated (and also dying) alveolar macrophages will not only recruit more macrophages as well as polymorphonuclear leukocytes (PMNs) and lymphocytes, but may also affect and activate bronchiolar and alveolar epithelial cells.

Reactive oxygen species can directly induce DNA damage (Knaapen *et al.*, 2002; Schins *et al.*, 2002b), and morphological transformations observed in Syrian hamster embryo (SHE) cells correlate well with the amount of hydroxyl radicals generated (Elias *et al.*, 2000, 2006; Fubini *et al.*, 2001). Neoplastic transformation was observed in in-vitro assays in the absence of secondary inflammatory cells (Hersterberg *et al.*, 1986; Saffiotti & Ahmed, 1995; Elias *et al.*, 2000). There seems to be no correlation between the extent of cytotoxicity as assessed by colony-forming efficiency and transforming potency (SHE test) when various quartz samples were investigated (Elias *et al.*, 2000). In contrast to transforming potency, which was clearly related to hydroxyl radical generation, cytotoxicity was not affected by antioxidants. Partial reduction of transforming potency when deferoxamine-treated quartz was used points to the role of transitional metals, e.g. iron on the particle surface in generating hydroxyl radicals (Fubini *et al.*, 2001). The SHE test used in this study by Fubini *et al.* (2001) and by others is recommended by the Centre for the Validation of Alternative Methods (ECVAM) as an alternative method for investigating the potential carcinogenicity of particulates (Fubini, 1998b). In nude mice injected with these transformed cells, tumours could be initiated (Saffiotti & Ahmed, 1995).

Particle uptake by target cells is also relevant for direct genotoxicity (Schins, 2002). Crystalline silica particles were detected in type II lung epithelial cells (RLE-6TN) *in vitro*; these particles were located also in close proximity to the nuclei and mitochondria, but not within these organelles. An osteosarcoma cell line lacking functional mitochondria was investigated with respect to quartz-related DNA damage with an osteosarcoma cell line with normal mitochondria. Only the cell line with functioning mitochondria showed significantly increased DNA damage after exposure to DQ12 quartz (Li *et al.*, 2007).

The relationship between genotoxic effects (formation of DNA strand breaks) and the uptake of quartz particles was investigated *in vitro* with A549 human lung epithelial cells (Schins *et al.*, 2002a). The percentage of A549 cells containing particles was clearly lower after exposure to quartz coated with polyvinylpynidine-*N*-oxide or aluminum lactate compared to uncoated quartz (DQ12). In this experiment, DNA strand breaks measured (Comet assay) in the exposed cells correlated very well with the number of particles absorbed by the cells. It could also be demonstrated that the generation of reactive oxygen species was closely related to the formation of DNA strand breaks (Schins, 2002). However, in other in-vitro studies using different quartz species, DNA strand breaks in epithelial cells could be observed only at particle concentrations that caused cytotoxicity (Cakmak *et al.*, 2004).

Rats were exposed to crystalline silica for 3 hours and sacrificed at different time points after exposure, and lungs were examined by electron microscopy. The lungs were fixed by vascular perfusion through the right ventricle. In these investigations, silica crystals were found within the cytoplasm of type I lung epithelial cells (Brody *et al.*, 1982). Although type I cells are not the target cell for tumour formation, these data show that the uptake of quartz particles in epithelial lung cells *in vivo* is in principle possible. Other particles including titanium dioxide, carbon black, or metallic particles have occasionally been found in type I lung epithelial cells in rats after inhalation exposure (Anttila, 1986; Anttila *et al.*, 1988; Nolte *et al.*, 1994).

After intratracheal instillation of DQ12 quartz, DNA strand breaks could be observed in lung epithelial cells isolated from quartz-treated rats. This effect was not found when the quartz dust was treated with either polyvinylpyridine-*N*-oxide or aluminium lactate. This finding suggests an important role of the reactive surface of quartz-induced DNA damage *in vivo*. No increase in alkaline phosphatase was found in the bronchiolo-alveolar lavage fluid of quartz-treated rats, and therefore, as alkaline phosphatase is an enzyme specifically present in type II epithelial cells, it can be assumed that there was no obvious cytotoxicity in these lung cells. These data support the current view of the important role of inflammatory cells in quartz-induced genotoxic effects (Knaapen *et al.*, 2002).

4.2.3 Depletion of antioxidant defences

Substantial amounts of ascorbic acid (Fenoglio *et al.*, 2000b) and glutathione (Fenoglio *et al.*, 2003) are consumed in the presence of quartz in cell-free tests via two different surface reactions. Both reactions may deplete antioxidant defences in the lung-lining fluid, thereby enhancing the extent of oxidative damage.

Incubation of murine alveolar MH-S macrophages with quartz particles (80 µg/cm^2) for 24 hours inhibited glucose 6-phosphate dehydrogenase (G6PD)-1 activity by 70%, and the pentose phosphate pathway by 30%. Such effects were accompanied by a 50% decrease in intracellular glutathione. Quartz inhibits G6PD but not other oxidoreductases, and this inhibition is prevented by glutathione, suggesting that silica contributes to oxidative stress also by inhibiting the pentose phosphate pathway, which is critical for the regeneration of reduced glutathione (Polimeni *et al.*, 2008).

4.2.4 Indirect mechanisms

After 13 weeks of inhalation exposure to 3 mg/m^3 crystalline silica (mass median aerodynamic diameter, 1.3 µm) or 50 mg/m^3 amorphous silica (mass median aerodynamic diameter, 0.81 µm), the percentage of PMNs in the lung of the exposed rats was similar after each exposure. However, HPRT mutation frequency of the alveolar epithelial cells was significantly increased only in rats exposed to crystalline silica. Other factors including toxic effects to epithelial cells, solubility, and biopersistence may also be important for the induction of these mutagenic effects (Johnston *et al.*, 2000). A specific finding in rats treated intratracheally with amorphous silica (Aerosil®150, pyrogenic silica with primary particle size of 14 nm) was a severe granulomatous alveolitis which over time progressed to "scar-like" interstitial fibrotic granulomas not seen after crystalline silica exposure in rats (Ernst *et al.*, 2002). Lung tumours were found in rats also after the repeated intratracheal instillation of the same amorphous silica (Kolling *et al.*, 2008).

Toxic mineral dusts, especially crystalline silica, have unique, potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (silicosis) and lung cancer (Hamilton *et al.*, 2008). Macrophages express a variety of cell-surface receptors that bind to mineral dusts leading to phagocytosis, macrophage apoptosis, or macrophage activation. The major macrophage receptor that recognizes and binds inhaled particles as well as unopsonized bacteria is MARCO (Arredouani *et al.*, 2004, 2005). Additional members of the macrophage-scavenger receptor family responsible for binding mineral particles as well as a wide range of other ligands include SR-AI and SR-AII (Murphy *et al.*, 2005). Although SR-AI/II and MARCO bind both toxic and non-toxic particles, only crystalline silica triggers macrophage apoptosis following

binding to these scavenger receptors (Hamilton *et al.*, 2008). Other receptors expressed by macrophages and other target cells in the lung that bind mineral dusts include complement receptor and mannose receptors (Gordon, 2002). The pathological consequences of silica-induced injury to alveolar macrophages followed by apoptosis is impaired alveolar-macrophage-mediated clearance of crystalline silica as discussed in Section 4.1. Lysosomal membrane permeabilization following phagocytosis of crystalline silica particles has been hypothesized to enhance IL-1β secretion (Hornung *et al.*, 2008), and to trigger the release of cathepsin D, leading to mitochondrial damage, and the apoptosis of alveolar macrophages (Thibodeau *et al.*, 2004). Macrophage injury and apoptosis may be responsible for the increased susceptibility of workers exposed to silica to develop autoimmune disease (Pfau *et al.*, 2004; Brown *et al.*, 2005), and pulmonary tuberculosis (IARC, 1997; Huaux, 2007).

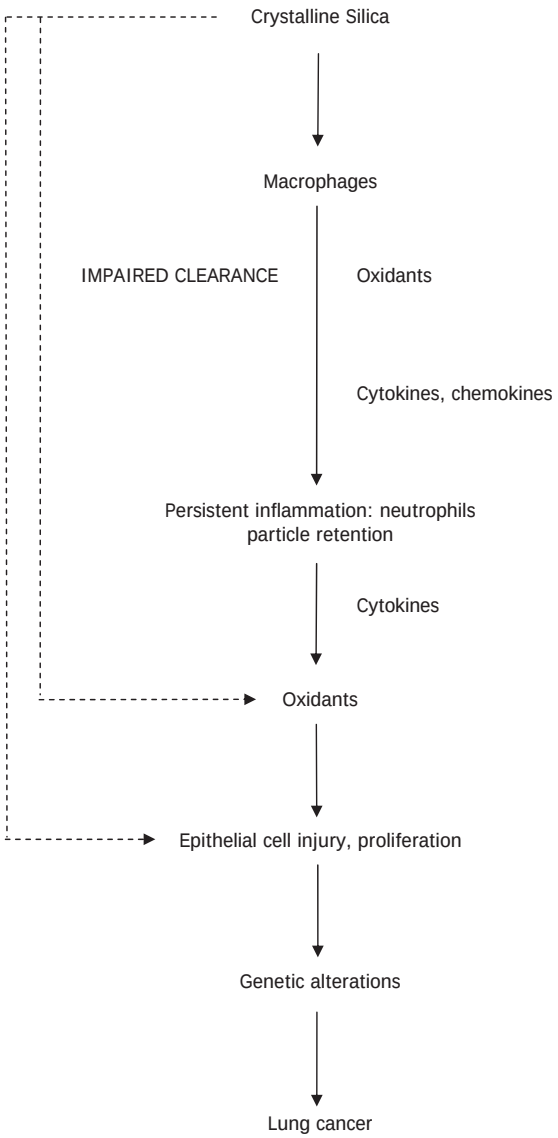
Persistent inflammation triggered by crystalline silica (quartz) has been linked to indirect genotoxicity in lung epithelial cells in rats, see Fig. 4.1 (IARC, 1997). Rats exposed to crystalline silica develop a severe, prolonged inflammatory response characterized by elevated neutrophils, epithelial cell proliferation, and development of lung tumours (Driscoll *et al.*, 1997). These persistent inflammatory and epithelial proliferative responses are less intense in mice and hamsters, and these species do not develop lung tumours following exposure to crystalline silica or other poorly soluble particles (IARC, 1997). There has been considerable discussion of whether the response of rats to inhaled particles is an appropriate model for the exposed response of humans (ILSI, 2000). Comparative histopathological studies of rats and humans exposed to the same particulate stimuli reveal more severe inflammation, alveolar lipoproteinosis, and alveolar epithelial hyperplasia in rats than in humans (Green *et al.*, 2007). These studies suggest that rats are more susceptible to develop persistent lung inflammation in response to particle inhalation than other species (ILSI, 2000).

Chronic exposure of rats to crystalline silica also leads to pulmonary fibrosis (Oberdörster, 1996), and workers with silicosis have an elevated risk of developing lung cancer (Pelucchi *et al.*, 2006). The causal association between chronic inflammation, fibrosis, and lung cancer was reviewed by IARC (2002). These associations provide a biological plausible mechanism between inflammation and the development of fibrosis and/or lung cancer (Balkwill & Mantovani, 2001).

4.3 Molecular pathogenesis of cancer of the lung

Acquired molecular alterations in oncogenes and tumour-suppressor genes characterize the multistage development of lung cancer (Sato *et al.*, 2007). Somatic alterations, such as DNA adducts, develop in the respiratory tract of smokers during the early stages of carcinogenesis (Wiencke *et al.*, 1999). Specific point mutations in in the *K-RAS* oncogene and the *p53* tumour-suppressor gene are considered as biomarkers of exposure to chemical carcinogens in tobacco smoke (Pfeifer *et al.*, 2002). Only one study has investigated the mutational spectrum of these genes that may be used as biomarkers for exposure to crystalline silica. Liu *et al.* (2000) analysed the mutation spectra in the *K-RAS* and *p53* genes in lung cancers that developed in workers with silicosis [smoking status unknown]. In a series of 36 cases, 16 mutations in exons 5, 7 and 8 of the *p53* gene were found. In contrast to non-occupational lung cancers, seven of these mutations clustered in exon 8. Most of the *K-RAS* gene mutations in non-small cell lung carcinomas occur at codon 12. Liu *et al.* (2000) did not detect this mutation in their case series of silicotics. Six mutations were found at codon 15 in exon 1 as well as additional mutations in codons 7, 15, 20, and

Fig. 4.1 Proposed mechanisms for the carcinogenicity of crystalline silica in rats



21. Most of these mutations were G→C transversions in contrast to G→T transversions at codon 12, which are characteristic of non-small cell lung cancers associated with tobacco smoking. If these specific mutations are confirmed in a larger series of lung cancers in silicotics, these could provide early biomarkers for the development of lung cancer in workers exposed to crystalline silica.

In a rat model of silica-induced lung cancer, a low frequency of *p53* gene mutations and no mutations in *K-RAS, N-RAS,* or *c-H-RAS* oncogenes were observed (Blanco *et al.*, 2007). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to crystalline silica.

The epigenetic silencing of the $p16^{INK4a}$ (Belinsky *et al.*, 2002), *CDH13,* and *APC* genes has also been found in a rat model of lung cancer induced by intratracheal instillation of crystalline silica (Blanco *et al.*, 2007). In this rodent model, the increased expression of iNOS

(inducible nitric oxide synthase) was also found in preneoplastic lesions, which is consistent with a role for reactive nitrogen species in silicosis (Porter *et al.*, 2006).

4.4 Species differences and susceptible populations

In rat chronic inhalation studies using crystalline silica or granular, poorly soluble particles, female rats are more susceptible than males to the induction of lung tumours. Overall, rats are susceptible to the induction of lung cancer following the exposure to crystalline silica or granular, poorly soluble particles, but hamsters and mice are more resistant. The mechanistic basis for these sex and species differences is unknown. Mice exposed to crystalline silica by intranasal instillation or subcutaneous injection, as well as rats injected intrapleurally or intraperitoneally develop lymphomas. Following inhalation exposure to crystalline silica, lymphomas have not been observed in any species (see Section 3).

In some workers exposed to crystalline silica, cytokine gene polymorphisms have been linked with silicosis (Yucesoy *et al.*, 2002). Specific polymorphisms in genes encoding in *TNF-α* and *IL-1RA* (interleukin-1 receptor antagonist) have been associated with an increased risk for the development of silicosis (Yucesoy & Luster, 2007). Gene–linkage analyses might reveal additional markers for susceptibility to the development of silicosis and lung cancer in workers exposed to crystalline silica.

4.5 Synthesis

Three mechanisms have been proposed for the carcinogenicity of crystalline silica in rats (Fig. 4.1). First, exposure to crystalline silica impairs alveolar-macrophage-mediated particle clearance thereby increasing persistence of silica in the lungs, which results in macrophage activation, and the sustained release of chemokines and cytokines. In rats, persistent inflammation is characterized by neutrophils that generate oxidants that induce genotoxicity, injury, and proliferation of lung epithelial cells leading to the development of lung cancer. Second, extracellular generation of free radicals by crystalline silica depletes antioxidants in the lung-lining fluid, and induces epithelial cell injury followed by epithelial cell proliferation. Third, crystalline silica particles are taken up by epithelial cells followed by intracellular generation of free radicals that directly induce genotoxicity.

The Working Group considers the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust. The mechanism responsible for the induction of lymphomas in rats and mice following direct injections of crystalline silica dust is unknown.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of quartz dust.

There is *limited evidence* in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust.

Crystalline silica in the form of quartz or cristobalite dust is *carcinogenic to humans (Group 1).*

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WOOD DUST

Wood dust was considered by a previous IARC Working Group in 1994 (IARC, 1995), although wood-related occupations (i.e. Furniture and Cabinet-making) had been considered by IARC Working Groups earlier, in 1980 and 1987 (IARC, 1981, 1987). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification, chemical, and physical properties of the agent

Wood dust, generated in the processing of wood for a wide range of uses, is a complex substance. Its composition varies considerably according to the species of tree being processed. Wood dust is composed mainly of cellulose (approximately 40–50%), polyoses, lignin, and a large and variable number of substances of lower relative molecular mass which may significantly affect the properties of the wood. These include non-polar organic extractives (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerides), polar organic extractives (tannins, flavonoids, quinones, and lignans) and water-soluble extractives (carbohydrates, alkaloids, proteins, and inorganic material) (IARC, 1995).

Trees are characterized botanically as gymnosperms (principally conifers, generally referred to as 'softwoods'), and angiosperms (principally deciduous trees, generally referred to as 'hardwoods'). Softwood and hardwood are not botanical concepts, referring to the species of tree and not directly describing the hardness of wood. Out of 12000 different species of trees, only about 800 are coniferous or softwoods, but roughly two-thirds of the wood used commercially worldwide belongs to the group of softwoods. Hardwoods tend to be somewhat more dense, and have a higher content of polar extractives than softwoods (IARC, 1995). For a comparison of softwoods and hardwoods, see Table 1.1.

For detailed descriptions of the classification and nomenclature, anatomical features, cell-wall structures, distribution of components of wood, and chemical components of wood, see the previous *IARC Monograph* (IARC, 1995), Nimz *et al.* (2005), and Kretschmann *et al.* (2007).

1.2 Occupational exposure

The wood species used in wood-related industries vary greatly by region and by type of product. Both hardwoods and softwoods (either domestically grown or imported) are used in the manufacture of furniture. Logging, sawmills, plywood, and particle-board manufacture generally involve the use of trees grown locally (IARC,

Table 1.1 Comparison of softwoods and hardwoods

Characteristic	Gymnosperms/conifers/softwoods	Angiosperms/deciduous wood/ hardwoods
Density (g/cm³)	White (silver) fir: mean, 0.41 (0.32–0.71) European spruce: mean, 0.43 (0.30–0.64) Scots pine: mean, 0.49 (0.30–0.86)	European beech 0.68 (0.49–0.88) European oak 0.65 (0.39–0.93)
Fibres	Long (1.4–4.4 mm)	Short (0.2–2.4 mm)
Cell type	One (tracheids)	Various
Cellulose	~40–50%	~40–50%
Unit	β-D-Glucose	β-D-Glucose
Fibre pulp	Long	Short
Polyoses	~15–30%	~25–35%
Unit	More mannose More galactose	More xylose
Lignin	~25–35%	~20–30%
Unit	Mainly guaiacyl	Mainly syringyl or guaiacyl
Methoxy group content	~15%	~20%
Extractive content		
Non-polar (e.g. terpenes)	High	Low
Polar (e.g. tannins)	Low	High

Reprinted in part from Volume 62 (IARC, 1995)

1995). For detailed descriptions of historical exposures to wood dust and other agents in the workplace, see the previous *IARC Monograph* (IARC, 1995).

1.2.1 Extent of occupational exposure

Kauppinen *et al.* (2006) used nearly 36000 exposure measurements to estimate the occupational exposure to inhalable wood dust by country, industry, the level of exposure and type of wood dust in 25 Member States of the European Union. In 2000–03, approximately 3.6 million workers in the European Union [and undoubtedly millions more worldwide] were exposed occupationally to inhalable wood dust. The estimated number of workers exposed by industry and the number exposed to a level exceeding 5 mg/m³ are shown in Table 1.2. The highest exposure levels were estimated to occur in the construction sector and furniture industry. Due to limited exposure data, there was considerable uncertainty in the estimates concerning construction woodworkers. About 560000 workers (16% of the number of workers exposed) may have been exposed to a level of inhalable wood dust that exceeded 5 mg/m³. Mixed exposures to more than one species of wood and dust from wooden boards was very common, but reliable data on exposure to different species of wood could not be retrieved.

The US National Occupational Exposure Survey, carried out during 1981–83 in the United States of America, estimated that about 600000 workers were exposed to wood dust. The largest numbers of exposed workers were employed in the building trades (n = 134090), and the lumber/wood product industries (n = 153543). Forestry workers (e.g. lumberjacks using chainsaws) were not considered to be exposed in this survey (NIOSH, 1990).

Table 1.2 WOODEX: Estimated number of workers exposed to wood dust in the 25 Member States of the European Union, 2000–03

Industry	Number employed	Number exposed	Exposed (% of employed)	Number exposed > 5 mg/m³
Construction	13 million	1.2 million	9	254000
Manufacture of furniture	1.2 million	713000	59	86500
Manufacture of joinery	472000	330000	71	42000
Forestry	445000	148000	33	< 100
Building of ships and boats	294000	31000	11	9600
Sawmilling	259000	196000	76	20000
Manufacture of other wood products	147000	97000	66	15500
Manufacture of wooden boards	124000	92000	74	8400
Manufacture of wooden containers	80000	57000	71	8600
All other employment	163 million	709000	0.4	118000
Total	179 million	3.6 million	2.0	563000

From Kauppinen *et al.* (2006)

1.2.2 Levels of occupational exposure

The highest exposures to wood dust have generally been reported in wood furniture and cabinet manufacture, especially during machine-sanding and similar operations (with wood dust levels frequently above 5 mg/m³). Exposure levels above 1 mg/m³ have also been measured in the finishing departments of plywood and particle-board mills, where wood is sawn and sanded, and in the workroom air of sawmills and planer mills near chippers, saws, and planers. Exposure to wood dust also occurs among workers in joinery shops, window and door manufacture, wooden boat manufacture, installation and refinishing of wood floors, pattern and model making, pulp and paper manufacture, construction carpentry, and logging. Measurements are generally available only since the 1970s, and exposures may have been higher in the past because of less efficient (or non-existent) local exhaust ventilation or other measures to control dust (IARC, 1995).

Woodworking machines have increased greatly in efficiency since the industrial revolution, and the increased speed of production has resulted in the generation of more dust. The increased efficiency may also result in exposure to finer wood dust particles than in the past, because smoother surfaces can be produced, and because saws and bits may retain their sharpness for longer. The introduction of engineering controls in some industries in some parts of the world, especially since the 1950s, has, however, reduced the exposure of workers considerably. Unfortunately, engineering controls, even if properly maintained, are not always effective, and the dust generated by hand-held power tools, particularly sanders, is much more difficult to control (IARC, 1995).

Studies published since the previous *IARC Monograph* reporting wood dust concentrations are presented in Table 1.3.

1.2.3 Particle size distribution

Chung *et al.* (2000) characterized the quantity, particle size distribution and morphology of dust created during the machining of medium-density fibreboard (MDF) in a controlled environment (a 2 × 2 × 2 m³ dust chamber). In terms of particle size distribution and morphology, the dust generated by machining MDF was generally found to be comparable with the dust generated by similarly machining hardwood or softwood. The quantity of dust generated during sanding

Table 1.3 Wood dust concentrations in various industries around the world

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m³)	Number of samples	Comments
Sawmills and lumber mills				
Demers *et al.* (2000), Teschke *et al.* (1999b) Softwood lumber mill British Columbia, Canada July–August 1996	Sawmill, planer mill, and yard	*Geometric mean (GSD)* Inhalable particulate: 1.0 (2.7) Estimated wood dust: 0.5 (3.1)	220	Exposure assessment conducted for cross-sectional study of respiratory health among 275 softwood lumber mill workers; mill processed spruce (*Picea engelmannii* and *glauca*), pine (*Pinus contorta*), and fir (*Abies lasiocarpa*); random sampling strategy; full-shift (7–8 hours) personal inhalable particulate samples collected using seven-hole inhalable dust samplers; wood dust exposure estimated using the resin acid content within dust in combination with observations of job tasks, proximity to dust sources and use of personal protective equipment
Rosenberg *et al.* (2002) Sawmill, Finland 1997–99	Sawhouse - pine processing - spruce processing	*Range of geometric means* Inhalable particulate: 0.5–2.2 Inhalable particulate: 0.4–1.9	237 (178 personal)	Measured exposure of 22 sawhouse workers in mills processing pine (*Pinus silvestris*) and spruce (*Picea abies*); full-shift area and personal inhalable particulate samples collected in breathing zone; exposure measured during evening shift on three consecutive days; IOM samplers to collect inhalable dust; gravimetric determination of inhalable dust; assumption that all or most of inhalable dust originated from wood dust
Hall *et al.* (2002), Sawmills British Columbia, Canada 1981–97	Lumber mill	*Geometric mean (GSD)* 0.72 (3.49)	1237	Analysis of compliance data set (and a nested subset of research data) containing personal exposure measurements to wood dust at 77 lumber mills; 23% of database were research samples, 77% were compliance samples; an empirical "determinants of exposure" model created using multiple linear regression

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m^3)	Number of samples	Comments
Rusca *et al.* (2008), Sawmill Switzerland June–October 2002	Sawmill	*Mean (range)* Inhalable particulate: 1.7 (0.2–8.5)	NR	Cross-sectional survey of male employees at 12 sawmills processing spruce and fir species in the French part of Switzerland; personal measurements of inhalable dust collected using IOM samplers; gravimetric analysis of inhalable dust
Miscellaneous wood-related occupations				
Edman *et al.* (2003) Wood pellets and briquettes Sweden	Industrial production of wood pellets and briquettes	*Geometric mean (range)* overall: 1.7 (0.16–19)	24	Personal exposure to wood dust measured gravimetrically and with personal data logging, real-time aerosol monitor; sampling time: 8 hours;
Kalliny *et al.* (2008) Wood-processing plants USA 1999–2004	Sawmill, plywood assembly plants, secondary wood milling operations, factories producing finished wood products	*Geometric mean (GSD)* Inhalable: 1.44 (2.67) Thoracic: 0.35 (2.65) Respirable: 0.18 (2.54)		Size-fractionated dust exposure surveyed longitudinally in 10 wood processing plants across the USA; dust exposures measured using the RespiCon Personal Particle Sampler; woods processed included softwoods (e.g. southern yellow pine and Radiata pine), hardwoods (red oak, maple, poplar, birch, rubber tree wood, cherry), engineered woods (medium-density fibreboard, particleboard), and plywood (from southern yellow pine)
Teschke *et al.* (1999a) Misc. establishments USA 1979–97		*Geometric mean (GSD)*	1632 personal TWA samples	Analysis of 1632 measurements of airborne wood dust reported to OSHA's Integrated Management Information System and development of an empirical predictive model; measurements collected using OSHA sampling method for "total" particulate (i.e. non-specific gravimetric method)
	Overall	1.86 (6.82)		
	Sanders, transportation equipment industry	17.5 (1.79)		
	Press operators, wood products industry	12.3 (4.12)		
	Lathe operators, furniture industry	7.46 (4.56)		
	Sanders, wood cabinet industry	5.83 (5.19)		

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m³)	Number of samples	Comments
Commonwealth of Australia (2008) Wood industries Australia	All wood industries	*Arithmetic mean (range)* 5.8 (0.06–210)	521	Analysis of existing surveillance data on inhalable wood dust exposure; data gathered via a review of published Australian literature; requests to government agencies, consultants, industry associations, specific industries and researchers; telephone surveys, and new air sampling
Alwis *et al.* (1999); Mandryk *et al.* (1999) Wood industries New South Wales, Australia 1996–97		*Geometric mean (GSD)* Inhalable dust		Personal inhalable and respirable samples collected; sampling time: 6–8 hours
	Logging	0.6 (1.3)	7	
	Sawmill	1.6 (3.2)	93	
	Wood chipping	1.9 (1.7)	9	
	Joinery	3.7 (3.7)	66	
		Respirable dust		
	Logging	< 0.1 (1.3)	4	
	Sawmill	0.3 (2.2)	31	
	Wood chipping	0.3 (1.7)	4	
	Joinery	0.5 (1.7)	39	
Scarselli *et al.* (2008) Wood industries Italy 1996–2006	All wood-related	*Geometric mean (GSD)* 1.0 (1.6)	10837	Analysis of airborne wood dust exposure measurements contained in the SIREP (Italian Information System on Occupational Exposure to Carcinogens) database; 10837 measurements on 10528 workers at 1181 companies; concentration of wood dust (hardwood or mixed wood dust) measured as 8-h TWA; no information about type of sample (personal vs stationary) or sampling strategy (random vs systematic)
Baran & Teul (2007) Wood processing Poland	Sawmill, manufacturing frames for furniture, and manufacturing ready-made furniture	*Range* 0.59–16.2		Analysis of measurements on 1100 workers employed in 9 wood-processing plants: 2 sawmills, 4 plants manufacturing frames for upholstered furniture, and 3 plants manufacturing ready-made furniture

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m^3)	Number of samples	Comments
HSE (2000); Black *et al.* (2007) Woodworking United Kingdom 1999–2000	Sawmilling, joinery, furniture manufacture, other	*Range of medians* 1.5–2.8	396	Cross-sectional survey of 46 representative companies in the British woodworking industry; personal samples collected as per MDHS 14/3; sampling time: 3–6 hours during activities judged to be representative of whole shift; gravimetric analysis of inhalable dust
Spee *et al.* (2007) Building projects the Netherlands 2002	Carpenters - overall Task-based - working indoors - working outdoors - indoors + outdoors	*Geometric mean (GSD)* 3.3 (2.1) *Arithmetic mean* 5.2 2.2 16.2	 44 29 11 4	Task-based exposure survey of 26 carpenters at 13 building projects from 12 companies; personal and area samples randomly collected as per specially designed protocol for sampling of wood dust in carpentry and furniture industry; gravimetric analysis of wood dust

GSD, geometric standard deviation; NR, not reported; OSHA, Occupational Safety and Health Administration; TWA, time-weighted average

was higher for sanding MDF when compared with sanding either hardwood or softwood. However, there was no significant difference with sanding MDF and natural woods, in terms of the quantity of dust generated.

Additional information on the particle size distribution of wood dust in workroom air can be found in the previous *IARC Monograph* (IARC, 1995).

1.2.4 Exposure to other agents

Within the furniture-manufacturing industry, exposure may occur to solvents and formaldehyde in glues and surface coatings. Such exposures are usually greatest for workers with low or negligible exposure to wood dust, and are infrequent or low for workers with high exposure to wood dust. Some outdoor furniture has also been manufactured from impregnated wood containing copper–chromium–arsenic compounds. Formaldehyde-based glues and varnishes were introduced in the wood industry after World War II but they became commonly used only in the 1950s and 1960s in most countries.

The manufacture of plywood and particle board may result in exposure to formaldehyde, solvents, phenol, wood preservatives, and engine exhausts. Sawmill workers may also be exposed to wood preservatives and fungal spores. Wood preservatives used include chlorophenol salts in sawmills, and organochlorine pesticides in plywood mills. When coniferous trees are sawn, monoterpenes evaporate into workroom air. In some sawmills, wood is also impregnated with copper–chromium–arsenic salts or creosote. Construction woodworkers may be exposed to asbestos and silica in their work environment. Many of them also varnish wooden floors with solvent- or water-based varnishes, some of which may release formaldehyde. Exposures to chemicals in industries where other wood products are manufactured vary, but are in many cases similar to those in the furniture-manufacturing industry (IARC, 1995).

1.2.5 Exposure of the general population

Woodworking is a popular hobby and non-occupational exposure may also occur during building and repair operations in homes. Woodworking can encompass a variety of activities that generate wood dust, including sawing, sanding, planing, routing, etc. The woods worked include a variety of particle boards, soft timbers, treated pine, masonite, plywood, and various imported hardwoods and softwoods. The size of the dust particles produced, the amount of dust, and resultant exposure to the person working in these areas depends on several factors including the equipment being used, the ventilation and extraction system in place, the state and type of timber, the general ventilation in the area, and any personal protective equipment that may be used. Exposure levels during non-occupational woodworking may be similar to those at workplaces, but the duration of exposure is usually substantially shorter.

2. Cancer in Humans

In the previous *IARC Monograph*, the evidence associated with exposure to wood dust or wood-related occupations or activites and cancer of the nasal cavity and paranasal sinuses (referred to below as 'sinonasal cancer'), and of the nasopharynx, larynx, lung, stomach, colon, and rectum as well as leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma was systematically reviewed because excesses had been observed in one or more studies. The Working Group for the previous *IARC Monograph* concluded that there was very strong evidence for sinonasal cancer. In case–control studies, they also consistently observed associations between exposure to wood

dust and cancer of the nasopharynx, but could not rule out confounding; and between wood dust and cancer of the larynx, but noted conflicting evidence from cohort studies. The Working Group concluded that there was "no indication that occupational exposure to wood dust has a causal role in cancers of the oropharynx, hypopharynx, lung, lymphatic and haematopoietic systems, stomach, colon, or rectum" (IARC, 1995).

Since the previous *IARC Monograph*, several studies have been published including selected case series of sinonasal cancer (see Table 2.1), cohort studies (see Table 2.2), registry-based studies (see Table 2.3). For case–control or other studies focused on particular cancer sites, only studies published since the previous volume that reported results for wood dust exposure are summarized here. The results of case–control studies on sinonasal, pharyngeal, and laryngeal cancer are summarized in Tables 2.4, 2.5, and 2.6, respectively. In addition, the results of case–control studies on lung cancer are summarized in Table 2.7, because of the relatively large number of studies that focus on this cancer site. Studies of other cancer sites are summarized in Table 2.8.

2.1 Sinonasal cancer

The Working Group for the previous *IARC Monograph* (IARC, 1995) reviewed a large number of case–control studies that consistently observed a strong association between exposure to wood dust or employment in wood-related occupations and sinonasal cancer. Support for this association was found in several large cohort studies of furniture workers (Olsen & Sabroe, 1979; Acheson *et al.*, 1984), but most cohort studies had little power to examine the risks for this cancer site (see Table 18, IARC, 1995). Odds ratios for all or unspecified sinonasal cancers were consistently elevated in case–control studies conducted in many countries (see Table 20, IARC, 1995).

Very high odds ratios were observed for sinonasal adenocarcinoma and strong evidence of a exposure–response relationship was observed in some studies (Hayes *et al.*, 1986; Olsen & Asnaes, 1986; Luce *et al.*, 1993) (see Table 21, IARC, 1995). In addition, an unusually large proportion of all adenocarcinomas in cases series were woodworkers. Some case–control studies observed an excess risk of sinonasal squamous cell carcinoma associated with wood dust or wood occupations, but the association was much weaker than was observed with adenocarcinoma (see Table 22, IARC, 1995). A pooled re-analysis of 12 case–control studies (including six of the nine above) found strong evidence for a exposure–response relationship among men for adenocarcinoma (OR, 0.6; 95%CI: 0.6–4.7 for low; OR, 3.1; 95%CI: 1.6–6.1 for moderate; and OR, 45.5; 95%CI: 28.3–72.9 for high wood dust), and little evidence for squamous cell carcinoma (OR, 0.9; 95%CI: 0.6–1.2 for low; OR, 1.0; 95%CI: 0.7–1.4 for moderate; and OR, 0.8; 95%CI: 0.4–1.6 for high wood dust) (Demers *et al.*, 1995a). For the three studies with results for squamous cell carcinoma not included in the pooled re-analysis, Fukuda *et al.* (1987) observed an excess among both male (OR, 2.9; 95%CI: 1.5–5.6) and female woodworkers (OR, 2.0; 95%CI: 0.3–14), Shimizu *et al.* (1989) observed an excess of squamous cell carcinoma of the maxillary sinus among male woodworkers (OR, 2.1; 95%CI: 0.8–5.3), and Olsen & Asnaes (1986) observed only a slightly increased risk of carcinoma of the sinonasal cavities among men classified as exposed to wood dust (OR, 1.3; 95%CI: 0.6–2.8).

Among the cohort studies that reported tree species, an excess of sinonasal cancer (SMR, 8.1; 95%CI: 3.7–16) was observed among British furniture workers exposed to hardwood dust (Rang & Acheson, 1981; Acheson *et al.*, 1984). No cases of sinonasal cancer were reported in a much smaller study of German furniture

workers exposed to beech, oak, and pine (Barthel & Dietrich, 1989) or among two small cohort of workers exposed to softwood—Finnish sawmill workers (Jäppinen *et al.*, 1989) and American plywood workers (Robinson *et al.*, 1990). [The Working Group noted that their power to detect an excess was low, and that exposure levels among sawmill and plywood workers were low compared to furniture workers.]

Few case–control studies in the previous *IARC Monograph* reported tree species. Very large excesses of sinonasal adenocarcinoma were associated with hardwood dust exposure in studies from France (OR, 5.30; 95%CI: 1.04–2.70, for highest level of exposure, Leclerc *et al.*, 1994) and Italy (OR, 0.90; 95%CI: 0.20–4.07, Battista *et al.*, 1983). Excesses of sinonasal cancer were observed among workers primarily exposed to softwood in case–control studies from Nordic Countries (OR, 3.3; 95%CI: 1.1–9.4, Hernberg *et al.*, 1983), the USA (OR, 3.1; 95%CI: 1.0–9.0 with 15-year lag, Vaughan *et al.*, 2000), Canada (OR, 2.5; $P < 0.03$, Elwood, 1981), and France (OR, 1.7, Leclerc *et al.*, 1994). The results for three of these four studies were restricted to squamous cell carcinoma.

Early case series reported many cases of sinonasal adenocarcinoma that were exposed to hardwoods (Acheson *et al.*, 1968, 1972; Leroux-Robert, 1974; Luboinski & Marandas, 1975; Andersen *et al.*, 1976, 1977; Engzell *et al.*, 1978; Kleinsasser & Schroeder, 1989). Seven cases of sinonasal squamous cell carcinoma exposed to "softwoods" were reported in a Norwegian case series (Voss *et al.*, 1985), and three cases of adenocarcinoma were reported among British workers exposed to softwoods (Acheson *et al.*, 1972). Several new case series have also been published with results relevant for the evaluation of sinonasal cancer (Table 2.1). Case series of sinonasal adenocarcinoma continue to make up a large proportion of cases with exposure to wood dust, with mean exposure durations ranging from 25 to 37 years. Most case series were restricted to adenocarcinoma, but in the case series that considered other tumours, the proportion of wood dust exposure was much less in the non-adenocarcinoma cases.

In the period following the previous *IARC Monograph* (IARC, 1995), five cohort studies (Table 2.2) were published that are relevant for the evaluation of wood dust, and three present results for sinonasal cancer. In a pooled re-analysis of five previously published cohort studies, Demers *et al.* (1995b) found an excess risk of sinonasal cancer among men classified as being definitely exposed to wood dust (SMR, 8.4; 95%CI: 3.9–16.0). Stellman *et al.* (1998) found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II. Innos *et al.* (2000) found an excess risk of sinonasal cancer among Estonian furniture workers highly exposed to wood dust (for men SIR, 2.3; 95%CI: 0.3–8.4, $n = 2$; for women SIR, 3.2; 95%CI: 0.1–18.1, $n = 1$).

Three new case–control studies (Table 2.4) have published results relevant for the evaluation of sinonasal cancer. Teschke *et al.* (1997) found no association with softwood or hardwood dust in a small Canadian study. In a pooled re-analysis of European case–control studies 't Mannetje *et al.* (1999) found a strong association with adenocarcinoma (OR, 12.2; 95%CI: 7.4–20.0), but no association with squamous cell carcinoma (OR, 0.7; 95%CI: 0.5–1.1). Pesch *et al.* (2008) found a strong association between adenocarcinoma and hardwood dust exposure (OR, 4.0; 95%CI: 1.9–8.3), but not with softwood dust exposure (OR, 0.3; 95%CI: 0.2–0.7). [The Working Group noted that only compensated cases were included, and this may have biased the results towards hardwood dust exposure.]

Table 2.1 Case series of sinonasal cancer according to occupation and exposure to wood dust

Reference, location, name of study	Sex	Origin	Histology	Exposed cases/ total cases	Occupations/exposures	Comments
Svane-Knudsen *et al.* (1998) Denmark	M, F	Nasal cavity and paranasal sinuses Hospital-based series 1978–95	Adenocarcinomas Epidermoid carcinomas	12/22 3/41	Hardwood dust exposure based on patient records [further details were not provided]	Softwood dust exposure not mentioned
Stoll *et al.* (2001) France	M, F	Ethmoidal sinuses 1975–2000	Adenocarcinomas	62/76	Exposed to wood dust	Mean duration of wood dust exposure 26 yr
Roux *et al.* (2002) France		Sinonasal cancer 1985–2001	Adenocarcinomas	134/139	Wood dust exposure from furniture, sawmill, carpentry and wood-product workers	Mean duration of wood dust exposure 30 yr
Barbieri *et al.* (2005) Italy	M, F	Ethmoidal sinuses 1978–2002	Adenocarcinomas	17/100	Hardwood and softwood dust exposure (5 softwood only)	
Liétin *et al.* (2006) France	M, F	Ethmoidal sinuses Hospital-based series 1985–2004	Adenocarcinomas	45/60	Wood dust exposure	Mean duration of wood dust exposure 25.6, range 2–44 yr
Fontana *et al.* (2008) France	M, F	Sinonasal cancer Diagnostic Registry 1981–2000	All	46/76 men 0/24 women	Wood dust exposure	Mean duration of wood dust exposure 37 yr
Llorente *et al.* (2008) Spain	M, F	Hospital-based series 1986–2002	All	62/79	Wood dust exposure	
Bornholdt *et al.* (2008) Denmark	M, F	Sinonasal cancer 1991–2001	Adenocarcinomas Squamous cell carcinomas	33/58 7/109	Wood dust exposure as per job title from the Central Person Registry or interview	
Choussy *et al.* (2008) France	M, F	Ethmoidal sinuses Hospital-based series 1976–2001	Adenocarcinomas	353/418	Wood dust exposure	Mean duration of wood dust exposure 27.7 yr

Table 2.2 Cohort studies of woodworkers exposed to wood dust

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1995b) Cohort mortality study United Kingdom and USA	Pooled analysis of updated data from 5 studies: British furniture workers (Acheson *et al.*, 1984), US furniture workers (Miller *et al.*, 1994), two cohorts of plywood workers (Blair *et al.*, 1990; Robinson *et al.*, 1995), and wood model makers (Roscoe *et al.*, 1992)	Workers classified as exposed to wood dust based on available work history	All cancers (140–208)	All woodworkers	1726	0.8 (0.8–0.8)	SMRs adjusted for sex, age, & calendar period using national rates	
			Pharynx (146–149)	All woodworkers	20	0.8 (0.5–1.3)		
			Nasopharynx (147)	All woodworkers	9	2.4 (1.1–4.5)		
				Possible wood dust	4	2.9 (0.8–7.5)		
				Probable wood dust	0	0.0 (0.0–3.8)		
				Definite wood dust	5	5.3 (1.7–12.4)		
			Paranasal sinus (160)	All woodworkers	11	3.1 (1.6–5.6)		
				Possible wood dust	1	0.8 (0.0–4.6)		
				Probable wood dust	1	1.2 (0.0–6.5)		
				Definite wood dust	9	8.4 (3.9–16.)		
			Larynx (161)	All woodworkers	18	0.7 (0.4–1.0)		
				Possible wood dust	4	0.4 (0.1–1.1)		
				Probable wood dust	8	1.1 (0.5–2.1)		
				Definite wood dust	6	0.8 (0.3–1.8)		
			Lung (162)	All woodworkers	575	0.8 (0.7–0.9)		
			Stomach (151)	All woodworkers	138	0.9 (0.8–1.1)		
			Intestine (152, 153)	All woodworkers	136	0.8 (0.6–0.9)		
			Rectum (154)	All woodworkers	60	0.8 (0.6–1.0)		
			Non-Hodgkin lymphoma (200, 202)	All woodworkers	57	1.1 (0.8–1.4)		
			Hodgkin disease (201)	All woodworkers	12	0.6 (0.3–1.1)		
			Multiple myeloma (203)	All woodworkers	33	1.3 (0.9–1.3)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1995b) (contd.)				Possible wood dust	9	1.0 (0.5–1.9)		
				Probable wood dust	8	1.3 (0.6–2.5)		
				Definite wood dust	11	1.6 (0.8–2.8)		
			Leukaemia (204–208)	All woodworkers	47	0.7 (0.5–0.9)		
Stellman *et al.* (1998) Prospective cohort USA	Prospective study of 362823 men enrolled in the American Cancer Society Cancer Prevention Study II in 1982 and followed up for 6 yr	Self-reported wood dust exposure or wood-related occupation	All causes (0–999)	Wood dust exposure	2995	1.1 (1.0–1.1)	RRs adjusted for age and smoking status	
				Wood occupation	1271	1.2 (1.1–1.2)		
			All cancers (140–208)	Wood dust exposure	961	1.1 (1.0–1.2)		
				Wood occupation	381	1.2 (1.1–1.3)		
			Pharynx (146–149)	Wood dust exposure	7	0.9 (0.4–2.0)		
				Wood occupation	2	0.8 (0.2–3.4)		
			Nasopharynx (147)	Wood dust exposure	1	0.4 (0.1–3.3)		
				Wood occupation	1	1.4 (0.4–1.8)		
			Paranasal sinus (160)	Wood dust exposure	1	1.1 (0.1–8.4)		
				Wood occupation	0			
			Larynx (161)	Wood dust exposure	8	1.6 (0.8–3.4)		
				Wood occupation	2	1.2 (0.3–4.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
(Stellman *et al.* (1998) contd.)			Lung (162)	Wood dust exposure	317	1.2 (1.0–1.3)		
				Wood occupation	111	1.1 (0.9–1.4)		
			Stomach (151)	Wood dust exposure	40	1.3 (1.0–1.9)		
				Wood occupation	11	1.1 (0.6–1.9)		
			Colon (153)	Wood dust exposure	100	1.0 (0.8–1.3)		
				Wood occupation	37	1.0 (0.8–1.5)		
			Rectum (154)	Wood dust exposure	23	1.3 (0.8–2.0)		
				Wood occupation	9	1.5 (0.8–2.9)		
			Non-Hodgkin lymphoma (200, 202)	Wood dust exposure	39	1.1 (0.8–1.5)		
				Wood occupation	12	1.0 (0.6–1.7)		
			Hodgkin disease (201)	Wood dust exposure	4	1.2 (0.4–3.4)		
				Wood occupation	1	1.0 (0.1–7.7)		
			Multiple myeloma (203)	Wood dust exposure	16	1.0 (0.6–1.8)		
				Wood occupation	4	0.7 (0.3–1.9)		
			Leukaemia (204–208)	Wood dust exposure	32	0.9 (0.6–1.3)		
				Wood occupation	14	1.1 (0.6–1.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) Retrospective cancer incidence cohort study Estonia	Retrospective study of incident cancers in all furniture workers employed in Tallinn, Estonia, for at least six months between 1 January 1946 and 31 December 1988 and living in Estonia on 1 January 1968. Cancer incidence follow-up: 1968–95	Exposure based on industrial hygiene surveys and work history	All cancers (140–208)	Med. exposure men	55	1.2 (0.9–1.6)	SIRs adjusted for age and calendar period	
				High exposure men	265	1.0 (0.9–1.1)		
				Med. exposure women	98	1.0 (0.8–1.2)		
				High exposure women	171	1.1 (0.9–1.3)		
			Buccal cavity (140–145)	Med. exposure men	5	3.7 (1.2–8.6)		
				High exposure Men	6	0.8 (0.3–1.7)		
				Med. exposure women	2	2.5 (0.3–8.9)		
				High exposure women	2	1.6 (0.2–5.8)		
			Pharynx (146–149)	Med. exposure men	3	4.0 (0.8–11.8)		
				High exposure men	6	1.5 (0.6–3.3)		
				Med. exposure women	0	0.0		
				High exposure women	0	0.0		
			Paranasal sinus (160)	Med. exposure men	0	0.0		
				High exposure men	2	2.3 (0.3–8.4)		
				Med exposure women	0	0.0		
				High exposure women	1	3.2 (0.1–18.1)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) (contd.)			Larynx	Men	7	0.7 (0.3–1.4)		
				Women	1	1.7 (0.0–9.4)		
			Bronchi and lung (162)	Med. exposure men	9	0.8 (0.4–1.5)		
				High exposure men	70	1.0 (0.8–1.3)		
				Med. exposure women	5	1.1 (0.4–2.6)		
				High exposure women	11	1.6 (0.8–2.9)		
			Stomach (151)	Med. exposure men	11	1.7 (0.9–3.0)		
				High exposure men	36	0.9 (0.6–1.2)		
				Med. exposure women	13	1.2 (0.7–2.1)		
				High exposure women	23	1.4 (0.9–2.1		
			Colon (153)	Med. exposure men	6	3.0 (1.1–6.7)		
				High exposure men	18	1.5 (0.9–2.4)		
				Med. exposure women	8	1.4 (0.6–2.7)		
				High exposure women	16	1.8 (1.0–2.9)		
			Rectum (154)	Med. exposure men	1	0.6 (0.0–3.2)		
				High exposure men	13	1.2 (0.7–2.1)		
				Med. exposure women	7	1.6 (0.6–3.2)		
				High exposure women	11	1.6 (0.8–2.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) (contd.)			Hodgkin disease (201)	Med. exposure men	1	2.6 (0.1–14.3)		
				High exposure men	3	1.4 (0.3–4.2)		
				Med. exposure Women	0	0.0		
				High exposure women	1	1.3 (0.0–7.5)		
			Haematopoietic and lymphatic (200–208)	Med. exposure men	2	0.8 (0.1–2.8)		
				High exposure men	14	0.9 (0.5–1.5)		
				Med. exposure women	5	1.0 (0.3–2.3)		
				High exposure women	3	0.4 (0.1–1.2)		
Szadkowska-Stańczyk & Szymczak (2001) Nested case–control study Poland	79 deceased lung cancer cases from a cohort of 10575 Polish pulp and paper mill workers (7084 men, 3491 women), 1+ yr, 1968–90, observed through 1995	Employment history obtained from the mills; occupational exposure was assessed by experts and a cumulative dose index	Lung (162)	Wood dust exposure	10	2.1 (0.9–4.9)	ORs adjusted for smoking. Matched on sex, birth year (± 1 yr), hire year (± 3 yr), and vital status	
				Low	4	2.1 (0.6–7.4)		
				Moderate & high	6	2.1 (0.7–6.3)		
				1–4 yr of exposure	4	1.7 (0.5–6.2)		
				5+ yr of exposure	6	2.4 (0.8–7.7)		
				Low cumulative dose	4	2.1 (0.5–9.2)		
				High cumulative dose	6	2.0 (0.7–5.4)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Dement *et al.* (2003) Cohort mortality study USA	13354 male carpenter members of the United Brotherhood of Carpenters and Joiners of America matched to the New Jersey State Cancer registry, who had participated in the New Jersey Carpenters fund before 1 July 2000 and matched to the New Jersey Carpenters Pension Fund All incident cancer cases within the cohort 1979–2000	Employment as a carpenter	All cancers (140–208)	All	592	1.1 (1.0–1.2)	SIRs adjusted for age and calendar period	The lowest duration of carpenter work (< 10 yr) was used as the comparison group for expected cases
			Pharynx (146–149)		11	1.4 (0.7–2.4)		
			Oesophagus (150)		8	1.1 (0.5–2.2)		
			Stomach (151)		12	1.0 (0.5–1.8)		
			Rectum (154)		35	1.5 (1.1–2.1)		
			Liver and gallbladder (155, 156)		12	1.6 (1.1–2.1)		
			Larynx (161)		14	1.2 (0.7–2.0)		
			Trachea, bronchus, and lung (160, 162)		137	1.5 (1.2–1.7)		
			Other respiratory (163–165)		15	4.2 (2.4–6.9)		
			Leukaemia (204–208)		12	0.8 (0.4–1.4)		
			Myeloma (203)		9	1.5 (0.7–2.8)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Lee *et al.* (2003) Cohort cancer incidence study Sweden	365424 male construction workers screened by the Organization for Working Environment, Occupational Safety and Health during 1971–93 and followed during 1971–99 through the Swedish National Cancer Registry	Wood dust exposure assessment based on a job–exposure matrix	Multiple myeloma (203)	Never exposed[1] Ever exposed[1] Never exposed[2] Ever exposed[2]	376 20 376 20	1.0 (reference) 0.8 (0.49–1.20) 1.0 (reference) 0.8 (0.49–1.23)	RR[1] adjusted for BMI at entry to cohort RR[2] adjusted for age, BMI, and other occupational co-exposures	
Jansson *et al.* (2005) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003) 260052 workers in cohort after excluding those missing smoking and BMI	Wood dust exposure assessment based on a job–exposure matrix	Oesophogus (adenocarcinoma) Gastric (cardia; adenocarcinoma) Oesophagus (squamous cell carcinoma)	No exposure Moderate exposure High exposure No exposure Moderate exposure High exposure No exposure Moderate exposure High exposure	61 3 0 152 11 2 170 8 1	1.0 (reference) 0.8 (0.2–2.5) 0 1.0 (reference) 1.1 (0.6–2.0) 4.8 (1.2–19.4) 1.0 (reference 0.7 (0.4–1.5) 2.2 (0.3–15.9)	IRRs adusted for attained age, calendar year at entry into cohort, tobacco smoking at entry to cohort and BMI at entry to cohort	

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Purdue *et al.* (2006) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003). 307779 workers in cohort after excluding those missing smoking	Wood dust exposure assessment based on a job–exposure matrix	All sites (140–208)	Never exposed	490	1.0	RRs adjusted for age, smoking status and snuff use	
				Ever exposed	20	0.7 (0.4–1.0)		
			Oral cavity (140–145)	Never exposed	166	1.0		
				Ever exposed	5	0.5 (0.2–1.2)		
			Pharynx (146–149)	Never exposed	108	1.0		
				Ever exposed	4	0.6 (0.2–1.6)		
			Larynx (161)	Never exposed	216	1.0		
				Ever exposed	11	0.8 (0.5–1.5)		
Sjödahl *et al.* (2007) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003). 256357 workers in cohort after excluding those missing smoking and BMI	Wood dust exposure assessment based on a job–exposure matrix	Gastric (non-cardia) (151)	Wood dust			RRs adjusted for age, smoking status and BMI	
				No exposure	892	1.0 (reference)		
				Moderate exposure	53	0.9 (0.7–1.2)		
				High exposure	3	1.2 (0.4–3.6)		

BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; RR, relative risk; SIR, standardized incidence ratio; standardized mortality ratio; yr, year or years

Table 2.3 Descriptive and linkage studies with results on exposure to wood dust

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Pukkala *et al.* (2009) Census cancer incidence linkage Nordic countries	All incident cancer cases diagnosed in Denmark (1961–2005), Finland (1961–2005), Norway (1961–2005), Sweden (1961–2005) and Iceland (1961–2005)	Woodworkers includes workers who prepare and treat wood and make, assemble and repair constructions and products of wood	All cancers (140–208)	Men	74353	0.95 (0.95–0.96)	SIRs adjusted for age and calendar period	National rates use to calculate expected cancers
				Women	3004	0.92 (0.89–0.95)		
			Pharynx (146–149)	Men	450	0.83 (0.76–0.11)		
				Women	8	0.94 (0.4–1.9)		
			Nose (160)	Men	355	1.8 (1.7–2.04)		
				Women	10	1.9 (0.9–3.5)		
			Adenocarcinoma	Men	122	5.5 (4.6–6.6)-		
				Women				
			Larynx (161)	Men	819	0.82 (0.77–0.8)		
				Women	7	1.7 (0.5–3.9)		
			Lung (162)	Men	10941	0.96 (0.94–0.97)		
				Women	235	1.2 (1.1–1.4)		
			Mesothelioma (158, 162.2)	Men	494	1.6 (1.4–1.7)		
				Women	11	2.1 (1.1–3.8)		
			Stomach (151)	Men	4904	1.04 (1.01–1.07)		
				Women	133	1.1 (0.93–1.3)		
			Colon (153)	Men	5478	0.9 (0.88–0.93)		
				Women	206	0.88 (0.77–1.01)		
			Rectum (154)	Men	3988	0.97 (0.94–1.0)		
				Women	123	0.96 (0.8–1.14)		
			Hodgkin disease (201)	Men	382	1.04 (0.94–1.15)		
				Women	5	0.47 (0.15–1.11)		
			Non-Hodgkin lymphoma (200, 202)	Men	2170	0.97 (0.933–1.02)		
				Women	110	1.03 (0.85–1.24)		
			Multiple myeloma (203)	Men	1263	1.01 (0.96–1.07)		
				Women	47	1.03 (0.76–1.37)		
			Leukaemia (204)	Men	1898	0.96 (0.92–1.01)		
				Women	61	0.93 (0.71–1.19)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Weiderpass *et al.* (2001) Census linkage study Finland	2833 cases of endometrial cancers and 1101 cervical cancers diagnosed since 1971 in a cohort of 413877 skilled and specialized workers in Finland excluding farming occupations	Occupations were coded into job titles and a national job–exposure matrix (FINJEM) converted each job title into a probability and mean level of exposure	Endometrium	Wood surface finisher	8	1.8 (0.8–3.5)	SIRs adjusted for birth cohort, follow-up period, and social class	
				Low wood dust exposure	368	1.0 (0.9–1.2)		
			Cervix	High wood dust exposure	70	1.1 (0.8–1.4)		
				Woodworker, NEC	7	2.5 (1.0–5.1)		
				Plywood and fibreboard worker	24	1.6 (1.0–2.3)		
				Low wood dust exposure	249	1.2 (1.0–1.4)		
				High wood dust exposure	34	1.2 (0.9–1.7)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Arias Bahia *et al.* (2005) Registry-based study Brazil	138 male cases in wood-related jobs based on hospital records, 1991–99, 20+ yr of age Expected numbers based on male incident rates from the Belem population-based cancer registry. 2420 deaths among woodworkers compared to other deaths in the State of Para	Employment as a wood worker	Oral cavity and pharynx		8	1.7 (1.0–2.6)	Age	PCIRs – proportional cancer incidence ratios Belem (1988–89)
			Stomach		32	1.0 (0.7–1.5)		
			Colon		1	0.3 (0.0–1.7)		
			Rectum		3	1.1 (0.2–3.7)		
			Nasal cavity		1	1.5 (0.0–8.5)		
			Larynx		7	1.2 (0.5–2.4)		
			Lung		18	1.2 (0.7–1.9)		
			Hodgkin disease		3	2.2 (0.4–6.3)		
			Other lymphomas		0	0.0		
			Multiple myeloma		2	2.4 (0.3–8.8)		
			Leukaemia		4	1.4 (0.4–3.5)		
			Oral cavity and pharynx		18	1.0 (0.6–1.7)		CMORs – cancer mortality odds ratios State of Para (1980–95)
			Stomach		82	0.8 (0.7–1.1)		
			Colon		5	0.5 (0.2–1.2)		
			Rectum		8	1.3 (0.6–2.8)		
			Larynx		18	1.3 (0.6–2.8)		
			Lung		53	0.8 (0.6–1.0)		
			Hodgkin disease		5	1.1 (0.4–2.8)		
			Other lymphomas		11	1.4 (0.7–2.6)		
			Multiple myeloma		1	0.5 (0.0–3.4)		
			Leukaemia		7	0.6 (0.2–1.2)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases /deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Laakkonen *et al.* (2006) Census linkage study Finland	Incident cancer cases in all economically active Finns born during 1906–45 who participated in the national population census on 31 December 1970 (667121 men; 513110 women)	Exposure to wood dust: None (0) Low (< 3 mg/m^3–yr) Med (3–50 mg/m^3–yr) High (> 50 mg/m^3–yr)	Nasal cavity (160)	None men	259	1.0 (0.9–1.1)	SIRs adjusted for age and social class	Exposure lag period 20 yr
				women	118	1.0 (0.8–1.2)		
				Low men	15	1.6 (0.9–2.6)		
				women	1	1.7 (0.0–9.7)		
				Med men	17	1.3 (0.8–2.1)		
				women	1	0.8 (0.0–4.4)		
				High men	1	1.2 (0.0–6.9)		
				women	0	0.0		
			Larynx (161)	None men	1965	1.0 (1.0–1.1)		
				women	128	1.0 (0.8–1.2)		
				Low men	76	1.1 (0.8–1.3)		
				women	1	1.2 (0.0–6.8)		
				Med men	77	0.7 (0.6–0.9)		
				women	3	2.1 (0.4–6.1)		
				High men	1	0.1 (0.0–0.7)		
				women	0	0.0		
			Lung (162)	None men	27309	1.0 (1.0–1.0)		
				women	3446	1.0 (1.0–1.0)		
				Low men	936	1.1 (1.0–1.2)		
				women	21	0.9 (0.6–1.4)		
				Med men	1784	1.0 (1.0–1.1)		
				women	48	1.0 (0.8–1.4)		
				High men	108	0.9 (0.7–1.0)		
				women	12	1.0 (0.5–1.7)		

CI, confidence interval; CMORs, cancer mortality odds ratios; PCIRs, proportional cancer incidence ratios; RR, relative risk; SIR,standardized incidence ratio; yr, year or years

2.2 Cancer of the nasopharynx

The previous *IARC Monograph* reviewed nine community-based case–control studies of cancer of the nasopharynx (see Table 25, IARC, 1995). The majority indicated an excess risk associated with either wood dust exposure (4/5 studies) or wood-related occupations (3/4 studies). Many of these studies had positive results based on very small numbers, and did not control for confounding. The studies were conducted in many different countries and odds ratios were generally in the range of 1.5–2.5. Among the studies that adjusted for the effects of smoking and alcohol, Vaughan (1989) and Vaughan & Davis (1991) observed an excess risk among carpenters (OR, 4.5; 95%CI: 1.1–19), and all woodworkers employed for 10 years or longer (OR, 4.2; 95%CI: 0.4–27). Sriamporn *et al.* (1992) observed an excess risk among wood cutters (OR, 4.1; 95%CI: 0.8–22).

None of the cohort studies reviewed by the previous *IARC Monograph* provided results for cancer of the nasopharynx, a rare tumour with an incidence rate of approximately 1/100000 in European countries.

In the period following the previous *IARC Monograph* (IARC, 1995), five new or updated cohort studies (Table 2.2) were published including a pooled re-analysis of five previously published cohort studies. Demers *et al.* (1995b) found an excess risk of cancer of the nasopharynx among workers classified as definitely exposed to wood dust (SMR, 5.3; 95%CI: 1.7–12.4, $n = 5$) and, overall, excesses were observed among both furniture (SMR, 2.4; 95%CI: 1.2–5.9, $n = 7$) and plywood workers (SMR, 4.6; 95%CI: 0.6–16.4, $n = 2$). Stellman *et al.* (1998) found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II. The remaining cohort studies did not present results for this organ site.

Three new case–control studies (Table 2.5) have published results relevant for the evaluation of cancer of the nasopharynx. Armstrong *et al.* (2000) observed an increased risk associated with wood dust among Malaysian Chinese workers (OR, 2.4; 95%CI: 1.3–4.2). Vaughan *et al.* (2000) in a population-based study observed no increased risk overall (OR, 1.2; 95%CI: 0.5–2.7), and no evidence of an exposure–response relationship in analyses by maximum or cumulative exposure in a multicentre study in the USA. In another population-based study Hildesheim *et al.* (2001) found an increased risk overall (OR, 1.7; 95%CI: 1.0–3.0), which increased with both duration and cumulative exposure in Taiwan, China. It was also reported that these results were not affected by further adjustment for formaldehyde. One further hospital-based study reported an excess for nasopharyngeal and sinonasal cancer combined (Jayaprakash *et al.*, 2008).

2.3 Cancer of the pharynx

The previous *IARC Monograph* reviewed four case–control studies of cancer of the pharynx other than the nasopharynx (see Table 26, IARC, 1995). Two indicated an excess risk associated with wood-related occupations, although one was based on very small numbers. Another found mixed evidence. None of the cohort studies reviewed by that Working Group provided relevant results.

Four new case–control studies (Table 2.5) published since the previous *IARC Monograph* have results relevant for the evaluation of cancer of the pharynx other than the nasopharynx. Gustavsson *et al.* (1998) observed a decreased risk for cancer of the hypopharynx associated with wood dust in Sweden (OR, 0.5; 95%CI: 0.3–1.0). Laforest *et al.* (2000) observed no increased risk overall (OR, 0.9; 95%CI: 0.5–1.7), and only a slightly increased risk in the highest categories of cumulative exposure (OR, 1.5; 95%CI: 0.6–3.9). Berrino *et al.* (2003) found an increased risk of

Table 2.4 Case–control studies of sinonasal cancer and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Teschke *et al.* (1997) Population-based case–control study Canada	Nasal cavity and paranasal sinus (160)	All incident cases with histologically confirmed primary malignant tumours age ≥ 19 yr; 1990–92	Controls were selected randomly from 5-yr age and sex strata of the provincial voters list; frequency-matched for age and sex	Occupational histories obtained by interview and occupational exposures assessed by job classification	Hardwood dust Softwood dust	0.6 (0.1–3.0) 0.7 (0.3–1.6)	Sex, age (< 60, 60–69, ≥ 70), cigarette smoking (0–19, ≥ 20 pack–years)	
't Mannetje *et al.* (1999) Pooled population-based case–control study Italy, France, Netherlands, Germany, Sweden	Nasal cavity and paranasal sinus (160)	555 cases (104 women, 451 men) from 4 studies in Italy and 1 each from the Netherlands, France, Germany, and Sweden	1705 controls (241 women, 1464 men) from the same studies	Occupational history and job–exposure matrices were applied for wood dust	Wood dust exposure: Women Men Adenocarcinoma Squamous cell carcinoma	 1.2 (0.3–4.5) 2.4 (1.8–3.2) 12.2 (7.4–20.0) 0.7 (0.5–1.1)	Age group and study centre. Sex and smoking where applicable	
Pesch *et al.* (2008) Industry-based case–control study Germany	Nasal cavity and paranasal sinus (160)	86 male cases of adenocarcinoma of the nasal cavity and paranasal sinuses identified among workers with a recognized occupational disease during 1994–2003	204 controls randomly recruited from recognized accidents and falls frequency-matched to controls for age with 60 yr cut-off. Controls were also employed in the woodworking industries	Cumulative and average wood dust exposure quantified with a job–exposure matrix based on wood dust measurements at recent and historical workplaces	High exposure to: Hardwood Softwood Particle board Medium-density fibreboard	 4.0 (1.9–8.3) 0.3 (0.2–0.7) 0.5 (0.3–1.0) 0.3 (0.1–1.1)	Smoking, age, region, ever exposed to varnishes or stains	Only cases with successful compensation claims were used

Table 2.5 Case–control studies of cancer of the pharynx and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Gustavsson *et al.* (1998) Population-based case–control study Sweden	Pharynx (140–149)	401 incident squamous cell carcinomas, men aged 40–79 yr living in Stockholm or Southern health care region, 1988–91	Randomly selected from the base population, frequency-matched on region and age group	Occupational history, exposure assessment based on literature survey of exposure	Ever exposed	0.5 (0.3–1.0)	Region, age, alcohol consumption, smoking habits	
Armstrong *et al.* (2000) Population-based case–control study Malaysia	Nasopharynx (147)	282 Chinese cases identified between July 1990 and June 1992 through diagnosis records and/or treatment at centres with radiotherapy in the study area of Selangor & the Federal Territory	Matched by age (± 3yr) to 1 control in good health with no history of cancer of the head, neck or respiratory system, selected from Chinese population	Occupational histories were obtained by interview, exposure based on job	Any history of occupational exposure to wood dust	2.4 (1.3–4.2)	Diet and cigarette smoke indices, and matched on age	
Vaughan *et al.* (2000) Multicentred population-based case–control study USA 1987–93	Nasopharynx (147)	196 newly diagnosed cases in men & women, age 18–74 yr, from 5 registries (Connecticut, Detroit, Iowa, Utah and western Washington)	244 controls from the general population through random-digit dialling and frequency-matched to the cases by age (± 5yr), sex and cancer registry	Lifetime histories of occupational and chemical exposures taken by interview; estimates of exposures assessed on a job-by-job basis	Ever exposed Max exposure (mg/m^3): > 0.0–0.55 > 0.55–1.50 > 1.50 Cumulative (mg/m^3–yr): > 0.0–2.75 > 2.75–15.70 > 15.70	1.2 (0.5–2.7) 1.3 (0.5–3.6) 2.0 (0.5–8.1) 0.2 (0.0–2.1) 0.7 (0.2–2.5) 3.0 (0.9–9.8) 0.4 (0.1–2.3)	Age, sex, race, SEER site, cigarette use, proxy status, education and cumulative exposure to formaldehyde	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Laforest *et al.* (2000) Hospital-based case–control study France 1989–91	Hypopharynx (148)	296 men, incident squamous cell carcinomas, histologically confirmed from 15 hospitals	Controls were patients with primary cancers of different sites requiring the same medical environment as case cancers, frequency-matched on age, same hospital or similar hospitals nearby, 1987–91	Detailed lifetime occupational history taken, occupational exposures were assessed through a job–exposure matrix	Ever exposed Probability: ≤ 70% > 70% Duration: < 6 yr 6–10 yr > 10 yr Cumulative: Low (< 10) Medium (10–42) High (> 42)	0.9 (0.2–4.1) 0.7 (0.3–1.8) 1.1 (0.5–2.3) 0.5 (0.2–1.5) 1.0 (0.3–2.9) 1.2 (0.5–3.0) 0.6 (0.2–1.6) 0.7 (0.3–2.3) 1.5 (0.6–3.9)	Age, smoking, alcohol, exposure to formaldehyde (yes/no), and mineral fibres (yes/no)	
Hildesheim *et al.* (2001) Population-based case–control study Taiwan, China July 1991 to December 1994	Nasopharynx (147)	375 newly diagnosed, histologically confirmed cases identified through two tertiary care hospitals in Taipei, Taiwan, China; < 75 yr of age, residents of Taipei city for 6+ mo	325 community controls matched to cases on sex, age and geographic residence by use of listings available through the National Household Registration System	Occupational history via interview, blindly assessed by an industrial hygienist for intensity and probability of exposure	Ever exposed Duration: ≤ 10 yr > 10 yr Cumulative: < 25 ≥ 25	1.7 (1.0–3.0) 1.2 (0.6–2.5) 2.4 (1.1–5.0) 1.2 (0.6–2.5) 2.4 (1.2–5.1)	Age, sex, education, ethnicity, and HLA	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Berrino *et al.* (2003) Population-based case–control study Italy, France, Spain, Switzerland 1979–82	Hypopharynx (148)	304 male incident cases from Calvados, France; Turin and Varese, Italy; Pamplona and Zaragoza, Spain; and Geneva, Switzerland	2176 male population controls	Occupational history through specialist interview; exposures assessed using a job–exposure matrix	< 55 yr of age: Possible exposure Probable exposure > 55 yr of age: Wood dust exposure	 0.3 (0.1–1.0) 0.4 (0.2–1.2) 2.1 (1.2–3.7)	Age, centre, tobacco, alcohol, diet, socioeconomic status, and exposure to other agents	
Vlajinac *et al.* (2006) Hospital-based case–control study Serbia & Montenegro 1998–2000	Oropharynx (146)	100 consecutive incident cases at the Clinical Centre of Serbia	100 controls among patients treated during the same period for non-malignant diseases of the head/neck, matched on age (± 2 yr), sex and place of residence	Occupational exposure to various chemicals, dust and other agents	Exposure to wood dust[1] Occupational exposure to wood dust[2]	2.3 (1.0–5.7) 4.2 (1.5–11.9)	[1]Education, BMI, smoking, alcohol, family history of cancers [2]Smoking, dental diseases, HSV infection, smoking, alcohol	
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Sinonasal & nasopharynx & hypopharynx (160, 147, 148)	90 incident cases in men diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure High exposure Occasionally exposed Regularly exposed	1.5 (0.9–1.5) 1.35 (0.4–4.6) 1.45 (0.85–2.5) 1.6 (0.75–3.3)	Age, sex, tobacco, education, year of enrollment	

BMI, body mass index; CI, confidence interval; HLA, human leukocyte antigen; HSV, herpes simplex virus; mo, month or months; yr, year or years

cancer of the hypopharynx among men over the age of 55 years (OR, 2.1; 95%CI: 1.2–3.7), and a decreased risk among men under 55 years (OR, 0.4; 95%CI: 0.2–1.2). Vlajinac *et al.* (2006) observed an increased risk of cancer of the oropharynx (OR, 2.3; 95%CI: 1.0–5.7) associated with wood dust in Serbia and Montenegro.

All five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the pharynx, although none provided results for subsites of other than the nasopharynx. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the pharynx than expected (SMR, 0.8; 95%CI: 0.5–1.3). Stellman *et al.* (1998) also found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II (RR, 0.9; 95%CI: 0.4–2.0). Innos *et al.* (2000) found an excess risk of cancer of the pharynx among Estonian furniture workers exposed to both medium levels (SIR, 4.0; 95%CI: 0.8–11.8) and high levels of exposure (SIR, 1.5; 95%CI: 0.6–3.3). Dement *et al.* (2003) observed slightly more cases of cancer of the pharynx than expected among members of the US carpenters union (SMR, 1.4; 95%CI: 0.7–2.4). Purdue *et al.* (2006) observed a somewhat reduced risk among Swedish construction workers exposed to wood dust versus those who were not (RR, 0.6; 95%CI: 0.2–1.6, $n = 4$).

2.4 Cancer of the larynx

The previous *IARC Monograph* reviewed ten case–control studies of cancer of the larynx (see Table 27, IARC, 1995). The majority had some indication of an excess risk associated with either wood dust exposure (1/2 studies) or wood-related occupations (7/8 studies), although sometimes based on small numbers. The studies were conducted in the USA ($n = 7$), Europe ($n = 2$), and the People's Republic of China ($n = 1$), and the majority of these studies adjusted for the effects of smoking. No support for this association was found in the cohort studies (see Table 18, IARC, 1995). The five cohort studies that reported results for cancer of the larynx observed fewer cancers than expected.

Seven new case–control studies (Table 2.6) have published results relevant for the evaluation of cancer of the larynx. Pollán & López-Abente (1995) in a Spanish study observed an excess risk among woodworkers (OR, 2.7; 95%CI: 0.9–7.7) that increased with duration of employment. Gustavsson *et al.* (1998) observed a decreased risk for cancer of the larynx associated with wood dust in Sweden (OR, 0.5; 95%CI: 0.3–0.9). Laforest *et al.* (2000) observed no increased risk overall and no evidence of an association with duration or cumulative exposure in a french study (OR, 1.0; 95%CI: 0.6–1.7). Elci *et al.* (2002) also found no association with wood dust in a Turkish study (OR, 1.1; 95%CI: 0.8–1.4). Berrino *et al.* (2003) found an increased risk of cancer of the larynx among men over the age of 55 (OR, 1.7; 95%CI: 1.2–2.6), and a decreased risk among men under 55 (OR, 0.6; 95%CI: 0.3–1.1). Ramroth *et al.* (2008) reported an excess based on a checklist (OR, 2.1; 95%CI: 1.2–3.9), but a weaker association based on a method using a job-specific questionnaire (OR, 1.4; 95%CI: 0.8–2.5). Jayaprakash *et al.* (2008) reported an excess among men based on self-reported exposure (OR, 2.1; 95%CI: 0.9–5.0). Six of the seven studies adjusted for the potential effects of smoking and alcohol consumption, but the last only adjusted for smoking.

All five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the larynx. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the larynx than expected (SMR, 0.7; 95%CI: 0.4–1.0), and no association with probability of exposure. Stellman *et al.* (1998) observed a potential excess risk associated with self-reported wood

Table 2.6 Case–control studies of cancer of the larynx and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Pollán & López-Abente (1995) Hospital-based case–control study Spain January 1982 to August 1985	Larynx (161)	50 male residents of Madrid with histologically confirmed squamous cell carcinomas diagnosed at Ramon y Cajal Hospital	1 hospital control (matched by sex, age, admission date excluding alcohol or tobacco-related conditions) and 1 population control (matched on sex, age, residential census sections at diagnosis)	Extensive job history up to 1 yr before diagnosis; subject was considered exposed at ≥ 1 yr of employment	All woodworkers 1–20 yr > 20 yr	2.7 (0.9–7.7) 1.6 (0.4–5.9) 5.6 (1.2–27.6)	Age, tobacco and alcohol consumption, and other occupational groups	
Gustavsson *et al.* (1998) Community-based case–control study Sweden 1 January 1988 to 31 January 1991	Larynx (161)	401 incident squamous cell carcinomas in all Swedish men aged 40–79 yr living in Stockholm or the southern health care region	Referents randomly selected from the base population and frequency-matched to the cases for region and age group (40–54, 55–64, 65–79 yr)	Exhaustive occupational history taken and exposure assessments were based on a literature survey of exposure data for different occupations	Ever exposed	0.5 (0.3–0.9)	Adjusted for region, age, alcohol consumption and smoking habits	

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Laforest *et al.* (2000) Hospital-based case–control study France 1 January 1989 to 30 April 1991;	Larynx (161)	296 primary incident squamous cell cancers diagnosed and histologically confirmed in 15 French hospitals; only men were included in the study	Controls were patients with primary cancers of different sites requiring the same medical environment as case cancers, selected by frequency matching on age and recruited between 1987 and 1991 in the same hospitals as the cases or similar hospitals nearby	Detailed lifetime occupational history taken and occupational exposures were assessed through a job–exposure matrix	**Wood dust** Ever exposed Probability of exposure: ≤ 70% > 70% Duration of exposure: < 6 yr 6–10 yr > 10 yr Cumulative level: Low (< 10) Medium (10–42) High (> 42)	 1.0 (0.6–1.7) 0.9 (0.4–2.0) 1.1 (0.5–2.2) 1.4 (0.6–3.2) 0.5 (0.2–1.5) 1.0 (0.5–2.3) 1.0 (0.4–2.1) 1.2 (0.5–2.8) 0.9 (0.3–2.3)	Age, smoking, alcohol, exposure to formaldehyde, and mineral fibres	
Elci *et al.* (2002) Hospital-based case–control study Turkey 1979–84	Larynx (161)	940 cases among men identified from patients admitted to the Oncology Treatment Center of the Social Security Agency Okmeydani Hospital in Instanbul	1519 referent patients with Hodgkin disease, soft tissue sarcoma, non-melanoma skin cancer, testis, bone and male breast cancer as well as a series of non-cancer subjects	Occupational history taken using a questionnaire, occupations coded and exposures assessed using a job–exposure matrix developed for occupational dusts	Wood dust exposure Low intensity Med intensity High intensity Low probability Med probability High probability	1.1 (0.8–1.4) 0.8 (0.5–1.4) 1.4 (1.0–1.9) 0.8 (0.4–1.4) 1.3 (1.0–1.7) 1.4 (0.7–2.5) 0.4 (0.2–0.9)	Age, smoking, and alcohol consumption	

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Berrino *et al.* (2003) Population-based case–control study Italy, France, Spain, Switzerland 1979–82	Endolarynx (161)	696 male incident endolarynx cases diagnosed in Calvados, France; Turin & Varese, Italy; Pamplona & Zaragoza, Spain; Geneva, Switzerland	2176 male population controls	Occupational history taken through specialist interview; occupational exposures assessed using a job–exposure matrix	< 55 yr of age: Possible exposure Probably exposure > 55 yr of age Wood dust exposure	 0.5 (0.2–1.1) 0.6 (0.3–1.1) 1.7 (1.2–2.6)	Age, centre, tobacco, alcohol, diet, socioeconomic status, and exposure to other agents	
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Larynx (161)	124 incident male cases diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure High exposure Occasionally exposed Regularly exposed	0.8 (0.5–1.3) 2.1 (0.9–4.96) 0.8 (0.4–1.4) 1.5 (0.8–2.8)	Age, sex, tobacco, education, year of enrollment	
Ramroth *et al.* (2008) Population-based case–control study South-western Germany 1998–2000	Larynx (161)	257 histologically confirmed incident larynx cancer cases in men and women diagnosed in Rhein-Neckar-Odenwald region	769 population controls	Occupational history taken through specialist interview; occupational exposures assessed using exposure substance check-list (SCL), detailed occupational history, supplementary job-specific questionnaires (JSQ)	SCL: Wood dust Hardwood dust Softwood dust JSQ: Wood dust Hardwood dust Softwood dust	 2.1 (1.2–3.9) 2.6 (1.3–5.2) 2.2 (1.1–4.2) 1.4 (0.8–2.5) 1.2 (0.6–2.5) 1.5 (0.7–2.8)	Adjusted for age, sex, tobacco, alcohol, education	

CI, confidence interval; RR, relative risk; yr, year or years

dust exposure (RR, 1.6; 95%CI: 0.8–3.4, *n* = 8), but not for wood occupations (RR, 1.2; 95%CI: 0.3–4.9, *n* = 2) among participants in the Cancer Prevention Study II. Innos *et al.* (2000) observed fewer cases of cancer of the larynx than expected (SIR, 0.7; 95%CI: 0.3–1.4) among male Estonian furniture workers. Dement *et al.* (2003) observed slightly more cases of cancer of the larynx than expected among members of the US carpenters union (SMR, 1.2; 95%CI: 0.7–2.0). Purdue *et al.* (2006) observed a somewhat reduced risk among Swedish construction workers exposed to wood dust versus those who were not (RR, 0.8; 95%CI: 0.5–1.5).

Recent registry-based studies also presented results for wood dust and cancer of the larynx. No excess was observed among woodworkers in a large Nordic census-based cancer incidence linkage study (Pukkala *et al.*, 2009). Arias Bahia *et al.* (2005) observed a slight excess of cancer of the larynx in a Brazilian cancer registry and mortality study. Laakkonen *et al.* (2006) found no relationship with wood dust exposure in a Finnish cancer registry study.

2.5 Cancer of the lung

The Working Group for the previous *IARC Monograph* reviewed 24 case–control studies of cancer of the lung (see Table 28, IARC, 1995). Roughly half had some indication of an excess risk associated with either wood dust exposure or wood-related occupations. The studies were conducted in North America (*n* = 11), Europe (*n* = 9), Asia (*n* = 3), and New Zealand (*n* = 1). No support for this association was found in the cohort studies (see Table 18, IARC, 1995). The seven cohort studies that reported results for cancer of the lung observed a similar number of cancers to that expected.

Three new case–control studies (Table 2.7) have published results relevant for the evaluation of cancer of the lung. Wu *et al.* (1995) observed an increased risk of non-small cell lung cancers among African- and Mexican-American men. Matos *et al.* (2000) observed an increased risk for lung cancer among sawmill workers, but not other woodworkers in Argentina. Barcenas *et al.* (2005) observed an excess of lung cancer associated with wood-related occupations or self-reported exposure in an American case–control study. All results were adjusted for smoking.

Four of the five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the lung. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the lung than expected (SMR, 0.8; 95%CI: 0.7–0.9). Stellman *et al.* (1998) observed a slight excess risk associated with self-reported wood dust exposure (RR, 1.2; 95%CI: 1.0–1.3), but not for wood occupations (RR, 1.1; 95%CI: 0.9–1.4) among participants in the Cancer Prevention Study II. Innos *et al.* (2000) observed an increased risk among highly exposed female (SIR, 1.6; 95%CI: 0.8–2.9), but not among male Estonian furniture workers (SIR, 1.0; 95%CI: 0.8–1.3). Dement *et al.* (2003) observed an excess among members of the US carpenters union (SMR, 1.5; 95%CI: 1.2–1.7). In a nested case–control study of Polish pulp and paper mill workers, Szadkowska-Stańczyk & Szymczak (2001) observed an excess of lung cancer associated with wood dust exposure (OR, 2.1; 95%CI: 0.9–4.9), but no evidence of an exposure–response relationship.

Recent registry studies also presented results for wood dust and lung cancer. A small excess was observed among women (SIR, 1.2; 95%CI: 1.1–1.4) but not among men (SIR, 0.96; 95%CI: 0.94–0.97) in a large Nordic census-based cancer incidence linkage study (Pukkala *et al.*, 2009). Arias-Bahia *et al.* (2005) observed mixed results in Brazil; a slight excess in the cancer registry study and a decreased risk in the mortality study. Laakkonen *et al.* (2006) found no relationship with wood dust exposure in a Finnish cancer registry study.

Table 2.7 Case–control studies of cancer of the lung and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Wu *et al.* (1995) Hospital-based case–control study USA	Lung (162)	113 African-American and 67 Mexican-American cases with newly diagnosed lung cancer recruited from the hospitals in Houston and San Antonio, Texas	270 healthy controls without prior histories of cancer from community centres, cancer screening programmes, churches and employee groups frequency-matched on age, ethnicity and sex	Occupational histories collected by interview, self-reported occupational exposure to wood dust	Wood dust exposure African-American: Non-small cell lung cancer Small cell lung cancer Mexican-American: Non-small cell lung cancer Small cell lung cancer	3.5 (1.4–8.6) 4.8 (1.2–18.5) 0.7 (0.0–12.4) 3.8 (0.8–17.4) 0.3 (0.0–6.2)	Age, sex, mutagen sensitivity, and pack–yr (smoking)	.
Matos *et al.* (2000) Hospital-based case–control study Argentina 1994–96	Lung (162)	199 male patients residents in the city or in the province of Buenos Aires and admitted for treatment in any of 4 hospitals of Buenos Aires city	393 controls; 2 male control subjects hospitalized for conditions unrelated to tobacco use during the same period, and residents in the same area, matched by hospital and age (± 5yr)	Occupational history obtained by interview; occupational exposure assessed by job–exposure matrix	Occupation in: Sawmills or wood mills Furniture Woodworkers (carpenters, cabinet-makers, machine operators)	 4.8 (1.2–19.0) 1.0 (0.4–2.2) 0.7 (0.3–1.5)	Age group, hospital, pack–yr and industries with $P < 0.05$	

Table 2.7 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Barcenas *et al.* (2005) Hospital-based case–control study USA July 1995 to October 2000	Lung (162)	1368 men and women with incident histologically confirmed lung cancer diagnosed at the University of Texas Cancer Center	1192 cancer-free enrollees of private multispecialty clinics; matched on gender and ethnic groups	Longest held occupation or industry, self-reported wood dust exposure obtained by interview; minimum of 1 yr	Wood related occupation/industry Self-reported wood dust exposure Occupation, industry, or self-reported exposure: Lung (adenocarcinoma) Non-small cell lung carcinoma (excluding adenocarcinoma) Small cell lung carcinoma	3.2 (1.5–6.9) 1.5 (1.2–2.1) 1.5 (1.0–2.1) 1.9 (1.3–2.7) 1.1 (0.5–2.3)	Adjusted for age, gender, ethnicity, smoking status, and place of residence	
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Lung (162)	809 incident male cases diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure High exposure Occasionally exposed Regularly exposed	1.1 (0.9–1.4) 2.15 (1.3–3.6) 1.1 (0.8–1.4) 1.7 (1.2–2.4)	Age, sex, tobacco, education, year of enrollment	

2.6 Other cancer sites

The results for other cancer sites were reviewed, but were less consistent than for the respiratory tract. The results for case–control studies for wood dust that were published subsequent to the previous *IARC Monograph* are presented in Table 2.8.

2.7 Furniture and cabinet-making industry

The Working Group also addressed the carcinogenic risk associated with the furniture and cabinet-making industry that was evaluated in the previous *IARC Monograph* Volume 25 (IARC, 1981), and reassessed in Supplement 7 (IARC, 1987) when it was classified as *carcinogenic to humans (Group 1)*. Since then, new studies and pooled analyses have strengthened the association between working in this industry and sinonasal and nasopharyngeal cancers, including Fukuda & Shibata (1988), Minder & Vader (1988), Magnani *et al.* (1993), Demers *et al.* (1995a, b) and Bouchardy *et al.* (2002). Such studies are listed among others published since 1980 in Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.9.pdf; Table to 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.10.pdf; Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.11.pdf; Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.12.pdf; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.13.pdf; Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.14.pdf; Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.15.pdf; and Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-10-Table2.16.pdf.

From reviewing the studies in Tables 2.9 to 2.16 together with the data on exposure to wood dust in Tables 2.1 to 2.8, the Working Group attributed the causal association between working in the furniture and cabinet-making industry and sinonasal and nasopharyngeal cancers to wood dust.

Another possible association observed in the industry included excesses of pleural malignant mesothelioma, which is most likely the result of asbestos exposure. Another possible excess of haematopoietic malignancies may be the result to other exposures such as solvents. Relevant results are presented in Tables 2.11, 2.13 and 2.15 (online), but the Working Group considered data for these sites to be inconsistent and inadequate for evaluation.

2.8 Synthesis

There is consistent and strong evidence from both case–control studies and large cohort studies that wood dust causes sinonasal cancer. Most of these studies do not specify the histology of the tumours. Among the case–control that specified histology, very large excess risks were observed for sinonasal adenocarcinoma and wood dust exposure. Case series have found a large proportion of adenocarcinoma cases to be woodworkers.

There is also weaker evidence that wood dust causes cancer of the nasopharynx. The majority of case–control studies observed an increased risk of cancer of the nasopharynx associated with wood dust exposure or with employment in wood-related occupations, although often based on small numbers. This is supported by the pooled re-analysis of cohort studies where a strong association was observed with probability of wood dust exposure. The primary confounder of concern was formaldehyde exposure, but in the pooled cohort study the probability of wood dust exposure, which would likely be inversely correlated with formaldehyde exposure, was

Table 2.8 Case–control studies of other cancers and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Fritschi & Siemiatycki (1996) Population-based case–control study Canada 1979–85	Non-Hodgkin lymphoma (200, 202)	3730 male cases aged 35–70 yr, resident in Montreal, histologically confirmed non-Hodgkin lymphoma, Hodgkin disease, or myeloma	533 colorectal, bladder, prostate, stomach, kidney, melanoma, pancreas and oesophageal cancer controls. 533 population controls selected by electoral lists or random-digit dialling	Occupational history obtained by interview or questionnaire	Wood dust exposure: Non-substantial Substantial	 0.5 (0.3–0.8) 0.8 (0.5–1.3)	Age, proxy status, income (quintiles), ethnicity	Results for wood dust only presented for non-Hodgkin lymphoma
Cocco *et al.* (1998) Census-linked case–control study USA 1984–92	Gastric cardia (151.1)	1056 cases of gastric cardia cancer were identified in men aged 25 yr or more using death certificates from 24 states	5280 control subjects were identified the same way but who died of non-malignant disease; 5:1 match on region, sex, race, and age	Usual occupation obtained from death certificates, exposure was assessed using a job–exposure matrix	Wood dust exposure: Unexposed All exposed Low level exposure Med level exposure High level exposure	 1.0 (reference) 0.8 (0.6–1.1) 0.9 (0.6–1.4) 0.7 (0.5–1.2) 1.0 (0.5–2.2)	Matched on region, sex, race, and age	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Cocco *et al.* (1999) Census-linked case–control study USA 1984–96	Stomach (151)	41957 deaths of stomach cancer aged 25+ yr using death certificates from 24 states	83914 controls who died of non-malignant disease; 2:1 match on region, sex, race, and age (± 5 yr)	Usual occupation obtained from death certificates, exposure was assessed using a job–exposure matrix	White men:		Matched on region, sex, race, and age	
					Med probability	0.9 (0.8–1.1)		
					High probability	1.0 (0.9–1.1)		
					Med intensity	1.0 (0.9–1.1)		
					High intensity	0.9 (0.7–1.1)		
					African-American men:			
					Med probability	1.0 (0.7–1.3)		
					High probability	0.9 (0.8–1.2)		
					Med intensity	1.1 (0.9–1.3)		
					High intensity	0.8 (0.6–1.0)		
					White women:			
					Med probability	0.7 (0.4–1.2)		
					High probability	0.8 (0.3–2.2)		
					Med intensity	0.9 (0.7–1.2)		
					High intensity	0.7 (0.3–1.6)		
					African-American women:			
					Medium probability	1.3 (0.5–3.8)		
					Medium intensity	0.9 (0.5–1.6)		
					High intensity	0.4 (0.1–3.4)		

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Mao *et al.* (2000) Registry-linked case–control study Canada 1994–97	Non-Hodgkin lymphoma (200, 202)	1469 histologically confirmed incident cases (764 men, 705 women) of non-Hodgkin lymphoma diagnosed in 8 Canadian provinces who were 20–74 yr of age	5073 controls frequency matched on age and sex randomly selected from within the same provinces via Provincial Health Insurance Plans, Property Assessment databases, or random-digit dialling	Home or work exposure to 17 chemicals was obtained through questionnaires or interviews	Wood dust exposure: Men Women Never exposed 1–6 yr exposure ≥ 7 yr exposure	 0.9 (0.8–1.1) 1.4 (1.0–2.0) 1.0 (reference) 1.2 (0.7–1.9) 1.7 (1.1–2.6)	10-yr age groups, province, BMI (< 20, 20–27, > 27), consumption of milk	
De Roos *et al.* (2001) Population-based case–control study Canada & USA 1992–94	Neuroblastoma	538 incident cases under 19 yr of age at 139 participating hospitals	504 cases were identified through random-digit dialling individually caliper-matched to cases on date of birth	Telephone interviews with parents for maternal and paternal occupational history. Self-reported exposure assessed by an industrial hygienist (IH)	Wood dust exposure: Paternal occupational exposure Self-reported exposure IH-reviewed exposure	 1.4 (0.8–2.3) 1.5 (0.8–2.8)	Child's age, maternal race, maternal age, and maternal education	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Briggs *et al.* (2003) Population-based case–control study USA 1984–88	Non-Hodgkin lymphoma (200, 202) Hodgkin disease (201)	1511 non-Hodgkin lymphoma, 343 Hodgkin disease cases diagnosed among African-American and white men born 1929–53, from Atlanta, Detroit, Connecticut, Iowa, Kansas, Miami, San Francisco, Seattle	1910 controls with no history of the selected cancer identified by random-digit dialling and frequency-matched by birth year, and geographic region of cancer registry	Occupational history collected by professional interviewers	Wood dust exposure: Non-Hodgkin lymphoma: African-American White Hodgkin disease: African-American White	 1.4 (0.7–2.8) 1.1 (0.9–1.3) 4.6 (1.6–13.3) 0.9 (0.7–1.3)	Age and cancer registry.	
Fritschi *et al.* (2005) Population-based case–control study Australia January 2000–August 2001	Non-Hodgkin lymphoma (200, 202)	Incident cases of non-Hodgkin lymphoma diagnosed in New South Wales or the Australian Capital Territory; aged 20–74 yr	Controls were randomly selected from the New South Wales and Australian Capital Territory Electoral Rolls, frequency matched on age, sex and region of residence	Lifetime occupational history obtained by telephone interview & mailed questionnaire. Exposure assessment done blindly by an occupational hygienist and a job–exposure matrix	Hardwood dust exposure: Non-substantial Substantial Softwood dust exposure: Non-substantial Substantial	1.5 (0.9–2.4) 1.7 (1.0–2.9) 1.2 (0.6–2.7) 1.6 (1.1–2.6) 1.7 (1.0–2.8) 1.6 (0.7–3.8)	Adjusted for age, sex, state and ethnic origin	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Pan *et al.* (2005) Registry-linked case–control study Canada 1994–97	Brain (191)	1009 incident cases of histologically confirmed primary brain cancer from 8 provinces	5039 population control subjects aged 20–76 yr collected in the same study area	Occupational history obtained through questionnaires. Self-reported exposure	Wood dust exposure: Men Women Both sexes	 1.3 (1.9–1.4) 1.1 (0.8–1.7) 1.2 (1.0–1.4)	Age, province of residence, education, alcohol intake, total energy intake, smoking pack–yr, and sex	
Fritschi *et al.* (2007) Population-based case–control study Australia January 2001–August 2002	Prostate (185)	606 histologically confirmed cases in Western Australia, aged 40–75 yr. 402 cases of benign prostatic hyperplasia identified from hospital records	471 controls aged 45–75 yr randomly selected from the Western Australia electoral roll August 2001–October 2002; frequency-matched on 5 yr age groups	Occupational history obtained by questionnaires and interviews. Exposure was assessed for each occupation by an occupational hygienist for probability, frequency and total dose.	Wood dust exposure: Prostatic cancer– Not exposed Non-substantial Substantial Benign prostatic hyperplasia– Not exposed Non-substantial Substantial	 1.0 (reference) 1.1 (0.8–1.4) 1.2 (0.5–2.6) 1.0 (reference) 1.1 (0.8–1.4) 0.8 (0.4–1.4)	Adjusted for age	

BMI, body mass index; yr, year or years

associated with nasopharyngeal cancer risk, and an excess was observed among both the furniture workers and plywood workers subcohorts.

There was weaker evidence for other sites such as the pharynx, larynx, and lung. Although positive associations were observed in some case–control studies, the pattern was not as consistent and not supported by positive findings in cohort studies.

The great majority of studies did not report on the specific tree species to which workers were exposed or whether exposure was due primarily to hardwoods or softwoods. The few studies that did address tree species were relevant only for the evaluation of sinonasal cancer. There is strong evidence for an association between sinonasal cancer and exposure to hardwood dusts, based on the results of the few studies that specifically assessed exposure to hardwoods and on the results of case series that identified specific tree species. Among the few case–control studies that assessed the relationship with softwoods, there was a consistent excess risk, but the magnitude of the excess was small in comparison to hardwoods, and the association was primarily with squamous cell carcinoma.

3. Cancer in Experimental Animals

Only a limited number of studies in experimental animals have been published on the carcinogenicity of wood dust. Studies described below include those summarized in the previous *IARC Monograph* (IARC, 1995) as well as studies published since.

3.1 Inhalation

3.1.1 Rat

An inhalation study to determine the carcinogenicity of inhaled oak wood dust with and without wood preservatives was conducted in rats. Six groups of 58–61 female F344 rats were exposed to: 1) 18 mg/m^3 of untreated oak wood dust; 2) wood preservatives containing 1 µg/m^3 lindane and 0.2 µg/m^3 pentachlorophenol (PCP); 3) oak wood dust treated with lindane and PCP; 4) 21 µg/m^3 of sodium dichromate; 5) oak wood dust treated with chromate (wood contained the equivalent of 39 µg/m^3 chromate); and, 6) 72 µg/m^3 of *N*-nitrosodimethylamine (positive control). A group of 115 rats were sham-exposed (negative control). Approximately 24 rats/group were exposed for 25 weeks and approximately 36 rats/group were exposed for their lifespan. The particle size was reported as 2–7 µm. The untreated wood dust contained up to 5 µg/m^3 of chromate. No respiratory tract tumours were observed in the negative controls. The positive control group of animals exposed for their lifespan had an incidence of 12/35 nasal cavity tumours. Respiratory tract tumours occurred less frequently in animals exposed for only 25 weeks than in those exposed for their lifespan. The only significant finding in rats exposed for 25 weeks was an increased incidence over controls of benign tumours of organs other than the respiratory tract in the group exposed to chromate aerosol alone. In the rats exposed to untreated oak wood for their lifespan, 2/36 rats developed malignant tumours of the respiratory tract (one in the oral cavity, one bronchial carcinoma, but none in the nasal cavity); there were no benign tumours of the respiratory tract. There was 1/37 animals exposed to wood dust treated with chromate stain, and 1/34 animals exposed to chromate aerosol for their lifespan that had a nasal cavity tumour, but none were found in the rats exposed to untreated wood dust (Klein *et al.*, 2001).

Sixteen female Sprague Dawley rats were exposed to 25 mg/m^3 of untreated beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 104 weeks. There were 16 untreated controls. In the 15 surviving exposed rats and 15 control rats, no respiratory tract

tumours were observed. Incidences of non-respiratory tract tumours did not differ between untreated and exposed rats (Holmström *et al.*, 1989).

Fifteen female Wistar rats were exposed to 15.3 mg/m^3 of beech wood dust (mass median aerodynamic diameter [MMAD], 7.2 µm; geometric standard deviation [GSD], 2.2) for 6 hours/day, 5 days/week, for 6 months, and were observed for up to 18 months. No respiratory tract tumours were found in exposed rats or in 15 untreated controls. The incidence of non-respiratory tract tumours did not differ between exposed rats and untreated controls (Tanaka *et al.*, 1991).

3.1.2 Hamster

One group of 12 and one group of 24 male Syrian golden hamsters were exposed to either 15 or 30 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for either 36 or 40 weeks, respectively. One group of 12 and one group of 24 animals served as untreated controls. No respiratory tract tumours were observed in the 12 animals exposed to 15 mg/m^3, but 1/22 animals exposed to 30 mg/m^3 had an unclassifiable infiltrating malignant nasal tumour (not significantly different from controls) (Wilhelmsson *et al.*, 1985a, b). [The Working Group noted that in the above inhalation studies, the size of the dusts was quite large, which might allow some deposition in the upper respiratory tract, but very little deposition in the lower respiratory tract. No measurement of deposition was made, so the actual exposure is unknown.]

3.2 Intraperitoneal injection

3.2.1 Rat

Female Wistar rats received three weekly intraperitoneal injections of beech wood dust [total dose reported as 250 or 300 mg/animal] suspended in saline, and were held for 140 weeks. No mesotheliomas or sarcomas were reported in the 52 rats examined (Pott *et al.*, 1989). [The Working Group noted the limited reporting of the study. No details on the number of starting animals or on particle size were given.]

3.3 Administration with known carcinogens or other modifying factors

3.3.1 Rat

Four groups of 16 female Sprague-Dawley rats were exposed 6 hours/day, 5 days/week for 104 weeks by inhalation to: air (control); 25 mg/m^3 untreated beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm); 14.9 mg/m^3 formaldehyde; or wood dust plus formaldehyde. Metaplastic or dysplastic lesions were observed in rats exposed to formaldehyde with or without wood dust, but the incidences between both groups were not statistically different. No such lesions were observed in control rats or in rats exposed to wood dust alone. No respiratory tract tumours were observed in rats exposed to wood dust or to wood dust plus formaldehyde (Holmström *et al.*, 1989).

Two groups of 20 male Wistar rats were exposed by inhalation to air (control); or 15 mg/m^3 of beech wood dust (MMAD, 7.2 µm; GSD, 2.2) for 6 hours/day, 5 days/week for 6 months. Thereafter, five rats per groups were exposed to 10.2 mg/m^3 of sidestream cigarette smoke for 2 hours/day, 5 days/week for 1 month. The experiment was terminated 18 months after the start of the exposures. No tumours of the respiratory tract were observed (Tanaka *et al.*, 1991).

3.3.2 Hamster

Two groups of 12 male Syrian golden hamsters were exposed by inhalation to air (control) or 15 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 36 weeks. Another two groups of hamsters were treated similarly but also received weekly subcutaneous injections of 1.5 mg *N*-nitrosodiethylamine (NDEA) for the first 12 consecutive weeks. No nasal tumours were observed in the four groups. Tracheal squamous cell papilloma incidences were: 1/7, controls; 0/8, wood dust; 3/8, NDEA; 4/8, NDEA plus wood dust (Wilhelmsson *et al.*, 1985a, b).

Two groups of 24 male Syrian golden hamsters were exposed by inhalation to air or 30 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 40 weeks. Another two groups of hamsters were treated similarly but received weekly subcutaneous injections of 3 mg NDEA for the first 12 consecutive weeks. No respiratory tract tumours were found in control animals. The incidence of these tumours did not differ between the groups treated with NDEA or NDEA plus wood dust (Wilhelmsson *et al.*, 1985a, b).

3.4 Exposure to wood dust extracts

In a lifetime experiment, four groups of 70 female NMRI mice weighing 25–30 g [age unspecified] received skin applications of a mutagenic fraction of a methanol extract of beech wood dust in 30 µL acetone twice a week for 3 months. Positive and negative controls were included in the study (Table 3.1). No effect on survival was observed between the treated groups and the negative control groups. A comparison between mice treated with wood dust extract and mice serving as negative controls indicated an overall carcinogenic effect ($P < 0.01$, χ^2 test) (Mohtashamipur *et al.*, 1989). [The Working Group also noted a dose-dependent increase in the incidence of skin squamous cell papillomas and carcinomas combined or papillomas alone.]

Four groups of 50 male and female Kunming mice were intragastrically administered 0, 1, 2 or 4 g/kg body weight of a water extract of birch wood dust, once a week for 5 weeks. Thereafter, mice were given 0.5% butylated hydroxytoluene for 3 weeks in the diet. The experiment was terminated at experimental Week 15. There was a dose-dependent increase ($P < 0.05$) in lung tumour incidence (0/50, 2/49, 4/48, 7/49, respectively), and multiplicity (0, 0.04, 0.15, 0.24 tumour/mouse, respectively). No significant increase was observed in a similar experiment using an organic extract of birch wood dust (He *et al.*, 2002).

3.5 Exposure to wood shavings

Studies directed at testing the potential carcinogenicity of cedar shavings were inadequate in that they did not have control groups (Vlahakis, 1977; Jacobs & Dieter, 1978).

3.6 Synthesis

Several of the studies investigating the carcinogenicity of inhaled wood dust in rats and hamsters used particles with relatively large MMADs, a design that would enhance deposition in the upper respiratory tract, including the nasal cavity. Despite this design, the results of the animal studies do not confirm the nasal carcinogenicity of wood dust observed in humans. No measurement of the actual deposition of wood dust in the respiratory tract was made, and therefore the amount of the exposure is unknown.

In one study in mice, a methanol extract of beech wood dust was tested by skin application. Although a dose-dependent increase in the incidence of skin tumours was observed, this result cannot be used in the evaluation of the carcinogenicity in experimental animals of wood dust per se.

Table 3.1 Study in mice exposed to mutagenic fractions of methanolic extracts of dust[a]

Tumour	Negative controls			Extract (g)				Benzo[*a*]pyrene (µg)	
	Untreated ($n = 43$)	Shaven ($n = 44$)	Shaven, acetone-treated ($n = 42$)	2.5 ($n = 43$)	5.0 ($n = 50$)	7.5 ($n = 46$)	10.0 ($n = 49$)	5 ($n = 43$)	10 ($n = 42$)
Skin squamous cell carcinomas	–	–	–	1	–	–	1[b]	1	15
Skin squamous cell papillomas	–	–	–	1	1	6	5[b]	2	5
Skin keratoacanthomas	–	–	–	–	–	1	–	–	2
Skin papillary cystadenomas	–	–	–	–	1	–	–	–	–
Sebaceous gland adenomas	–	–	–	–	–	–	–	2	–
Mammary gland adenocarcinomas	–	–	–	–	4	3	2	1	1
Mammary gland adenoacanthomas	–	–	–	–	–	–	1	–	–
Mammary gland mixed tumours	–	–	–	–	–	–	2	–	–
Fibrosarcomas	–	–	–	–	–	1	–	–	–
Haemangiosarcomas	–	–	–	–	1	–	–	–	–
Neurofibrosarcomas	–	–	–	–	1	–	–	–	–
Lymphomas	–	–	–	–	–	–	1	–	–
Anaplastic carcinomas	–	–	–	–	1	–	–	–	–
Precancerous skin lesions	–	1	2	2	4	8	6	13	18

[a] Dust from untreated, semidry beech wood

[b] [$P < 0.01$; Cochran-Armitage test for trend] where comparisons are made for 0 (acetone-treated controls), 2.5, 5.0, 7.5 and 10 g extract groups, including squamous cell carcinomas and papillomas combined, or papillomas alone

Adapted from Mohtashamipur *et al.* (1989), numbers of animals given are effective numbers

4. Other Relevant Data

4.1 Deposition and clearance of particulates in the nasal region

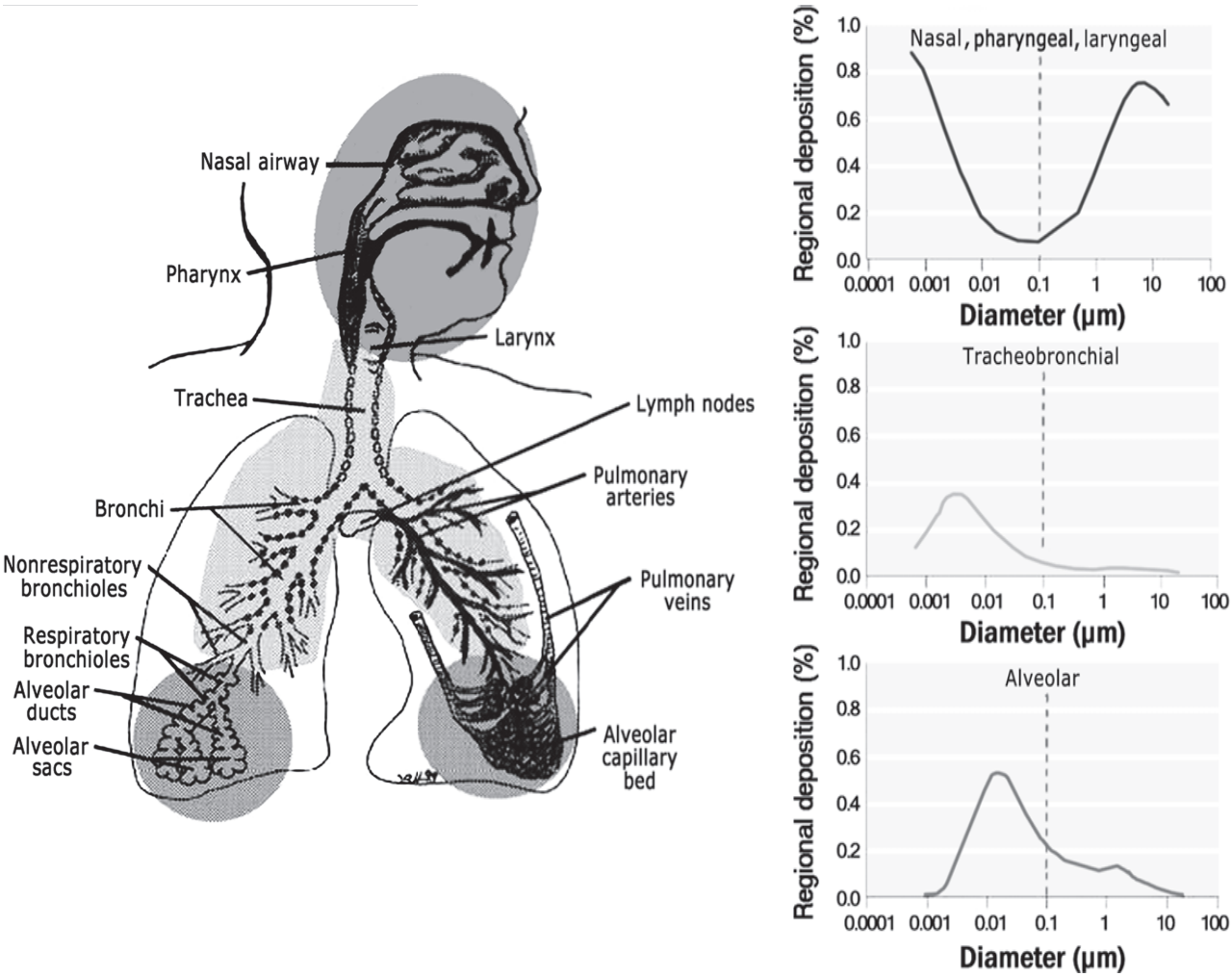
The anatomy and physiology of the upper respiratory tract is complex, and there are significant differences between rodents, non-human primates, and humans (reviewed by Stuart, 1984; Harkema, 1991). Wood dust, leather dust, and metal-containing dusts are complex mixtures that have been associated with the development of sinonasal and nasopharyngeal cancers in humans (IARC, 1995). The nasal region is a primary target of inhaled toxicants. In humans, the particulate fraction of wood and leather dusts is considered to be responsible for carcinogenesis (Fu *et al.*, 1996; Feron *et al.*, 2001). Particulate dosimetry in the upper respiratory tract depends on anatomy, airflow dynamics, and histology. Three-dimensional models have been developed to facilitate interspecies comparisons (Anjilvel & Asgharian, 1995). Humans vary in their breathing patterns at rest and at work; these patterns have an impact on the extent of nasal deposition of particles. In humans, coarse particles (2.5–10 µm) deposit by impaction in the nasal region; very fine particles (less then 0.01 µm in diameter) deposit in the nasopharynx by diffusion (Fig. 4.1; reviewed in Oberdörster *et al.*, 2005). Coarse particles deposited in the nose are rapidly removed by sneezing, sniffing, and mucociliary clearance. However, some areas in the nasopharynx lack cilia, and particles deposited in these regions have longer retention times that can be up to several days (Feron *et al.*, 2001).

4.2 Molecular pathogenesis

The histopathological classification of cancers arising in the sinonasal region (nasal cavity and paranasal sinuses) and in the nasopharynx varies with the anatomical location and associated risk factors (Rosai, 2004). In the sinonasal region, benign tumours or sinonasal papillomas occur; the inverted papilloma subtypes may progress to malignant squamous cell carcinomas in 3–13% of cases (Littman & Vaughan, 2006). The most common malignant tumour in the sinonasal region is squamous cell carcinoma, which is usually associated with cigarette smoking ('t Mannetje *et al.*, 1999), and rarely following exposure to wood dust (see Section 2). Adenocarcinomas are strongly associated with exposure to wood and leather dusts (Fu *et al.*, 1996; d'Errico *et al.*, 2009). Wood dust exposure was associated with a 21-fold [95%CI: 8.0–55.0] increase in the risk of having a sinonasal adenocarcinoma or a squamous cell carcinoma compared to not being exposed (Bornholdt *et al.*, 2008). These occupationally related carcinomas have a unique histological appearance described as intestinal-type sinonasal adenocarcinoma (ITAC). The majority of ITACs are localized in the superior nasal cavity and ethmoid sinus. This cancer develops after a long latent period of 20–30 years of exposure to wood dust, and is locally invasive with rare distant metastases (Llorente *et al.*, 2009). Other malignant sinonasal cancers include cylindrical (transitional) cell carcinoma, small cell neuroendocrine carcinoma, and undifferentiated (anaplastic) carcinoma (Rosai, 2004).

In the nasopharynx, the histopathological classification varies with age and associated risk factors (Yu & Yuan, 2006). Keratinizing squamous cell carcinomas occur at older ages, and the majority of nasopharyngeal carcinomas are non-keratinizing carcinomas, either differentiated or undifferentiated (Rosai, 2004). Non-keratinizing nasopharyngeal carcinomas are more common in high-risk populations in association with Epstein-Barr virus infection and other risk factors as discussed in Section 4.4.

Fig. 4.1 Deposition of inhaled particles in the human respiratory tract during nasal breathing



From Oberdörster *et al.*, (2005). Drawing courtesy of J Harkema. Reproduced with permission from Environmental Health Perspectives.

4.2.1 Cancer of the nasal cavity and paranasal sinuses

These cancers are extremely rare with only an overall annual incidence of approximately 1/100000 in Europe (Muir *et al.*, 1987). There have been few studies of molecular and genetic alterations associated with the development of sinonasal cancers, and no link to chemical carcinogens has been established (Saber *et al.*, 1998). Inverted papilloma is recognized as a preneoplastic lesion, and mutations in the *p53* tumour-suppressor gene have been associated with progression to squamous cell carcinoma. Epigenetic alterations characterized by promoter hypermethylation have also been identified in sinonasal papilloma (Stephen *et al.*, 2007). In ITACs of patients with known long-term exposure to wood or leather dust, $p14^{ARF}$ and $p16^{INK4a}$ promoter methylation was detected in 80% and 67% of cases, respectively (Perrone *et al.*, 2003). In the same study, *p53* mutations were present in 44% (7/16 cases) of the ITACs, and in all but one case the mutations were G:C→A:T transitions in 86% of the cases, and involved the CpG dinucleotides in 50% of the cases. Loss of heterozygosity at chromosomal loci encoding the *p53* (locus 17p13), $p14^{ARF}$ and

p16^{INK4a} (locus 9p21) genes were also reported in 58% and 45% of the cases, respectively (Perrone *et al.*, 2003). *p53* Mutations were previously reported in only 18% (2/11) of sinonasal adenocarcinomas from patients with unknown exposure (Wu *et al.*, 1996). *K-RAS* mutations were also reported in ITACs with a frequency of 13%, whereas the frequency was very low (1%) in squamous cell carcinoma (Saber *et al.*, 1998; Bornholdt *et al.*, 2008). Strikingly, among the five mutations located in codon 12 of the *K-RAS* gene, the G→A transition was the most common, and was present in tumour tissue (adenocarcinoma) from two wood-dust-exposed patients and from one patient with unknown exposure (Bornholdt *et al.*, 2008). [The Working Group noted that a clear link between exposure to wood or leather dust and specific G:C→A:T transitions in ITACs remains to be demonstrated.] Although ITACs resemble colonic adenocarcinomas histologically, alterations in *E-cadherin* and *β-catenin* genes characteristic of the APC pathway and alterations in mismatch-repair genes are rare in sinonasal adenocarcinomas (Perez-Ordonez *et al.*, 2004).

Unique patterns of chromosomal gains and losses have been associated with wood-dust-related ITACs (Korinth *et al.*, 2005; Llorente *et al.*, 2009). Overexpression of c-erbB2 protein was found in one-third of cases (Gallo *et al.*, 1998).

There are no identified precursor lesions leading to the development of ITACs, although hyperplasia, squamous metaplasia, and dysplasia occur frequently in areas adjacent to sinonasal carcinomas (Llorente *et al.*, 2009). A morphological study of nasal biopsies from 139 leather workers employed for a median of 29 years revealed squamous metaplasia in 65% of cases, dysplasia in 41% of cases, and goblet cell hyperplasia in 22% of cases. The presence of goblet cell hyperplasia was associated with longer occupational exposures in leather-tanning activities (Palomba *et al.*, 2008).

4.2.2 Cancer of the nasopharynx

There are few studies of molecular alterations in cancer of the nasopharynx. Many genetic alterations (chromosomal gains and losses) have been described in endemic nasopharyngeal carcinomas, but none of these changes have been specifically linked to wood or leather dust exposure (Hui *et al.*, 1999; Chan *et al.*, 2002).

4.3 Mechanisms of toxicity and carcinogenicity

4.3.1 Tissue injury

Histopathological changes associated with tissue injury and repair (metaplasia, hyperplasia) are extremely common in the upper respiratory tract of experimental animals and humans. In rats, the inhalation of a wide range of volatile and semi-volatile industrial chemicals induces tissue injury, inflammation, and hyperplasia; however, there is no consistent association with subsequent development of nasal cancer. Inflammation, IgE-mediated allergic rhinitis associated with the inhalation of particulate antigens, and inflammatory sinonasal polyps are very common in humans, yet sinonasal cancers are rare as discussed in Section 4.2. Common histopathological changes found in the nasal epithelium include cuboidal and squamous metaplasia and hyperplasia of goblet cells and cylindrical cells. These reactive changes are not considered to be precursors for the development of neoplasia. It is possible that wood dust particles incite tissue injury by direct mechanical damage, although there are no experimental data to support this mechanism (Feron *et al.*, 2001).

4.3.2 Impaired ciliary clearance and mucostasis

Heavy occupational exposure to wood dust has been reported to impair ciliary clearance, and to contribute to mucostasis (IARC, 1995). Theoretically, the impaired clearance of wood dust particles could lead to prolonged contact with the upper respiratory epithelium (Littman & Vaughan, 2006). Impaired mucociliary clearance may also allow particulate antigens to gain entry to nasal-associated lymphoid tissues, and enhance allergic sensitization (Feron *et al.*, 2001).

4.3.3 Direct genotoxicity

Direct genotoxic effects of wood dust extracts were summarized in IARC (1995). Overall, the mutagenic activity of beech and oak wood extracts was detected in bacterial systems and in rat hepatocytes *in vitro*. Several chemicals were isolated from wood extracts, but only quercetin and Δ^3-carene were shown to be mutagenic (IARC, 1995). Exposure to hexavalent chromium has been associated with the development of sinonasal cancers (Sunderman, 2001).

Dust particles may act as carriers for genotoxic agents. Chromium compounds are often present in oak and beech dusts as they are frequently used in the wood-processing industry, particularly as potassium dichromate in stains as well as fixing agents in wood preservatives. Stained furniture is made largely from oak and beech as they contain enough tannic acid to allow for chemical staining (Klein *et al.*, 2001). Nasal tumours were produced in rats following the inhalation of chromate-stained oak wood dust Klein *et al.* (2001). It was hypothesized that chromate trapped in dust particles is slowly released as hexavalent chromium in the nasal mucosa. Leather workers and tanners are also exposed to hexavalent chromium (Stern *et al.*, 1987). Hexavalent chromium is genotoxic and has been linked with the development of sinonasal cancers in humans (Table 4.1; IARC, 1990).

Table 4.1 Other risk factors for cancers of the nasal cavity and paranasal sinuses[a]

Exposure	Reference
Boot and shoe manufacture and repair	IARC (1987, 2012b)
Formaldehyde	IARC (1995, 2012d)
Hexavalent chromium	IARC (1990, 2012b)
Mineral oils	IARC (1987, 2012d)
Mustard gas	IARC (1987, 2012d)
Selected nickel compounds	IARC (1990, 2012b)
Tobacco smoking	IARC (2002, 2012c)

[a] All classifed as Group 1 carcinogens by IARC

DNA damage (detected by comet assay) in peripheral blood leukocytes was studied in 35 furniture workers and in 41 control office workers. Approximately 20% of woodworkers had elevated levels of DNA damage that did not depend on smoking status compared to 13% of control smokers and 7% of control non-smokers (Palus *et al.*, 1999). [The Working Group noted that the significance of this study is difficult to assess because DNA damage in the sinonasal mucosa was not studied.]

Another group of 60 male furniture workers occupationally exposed for more than 5 years to a mixture of softwood and hardwood dusts (7.4–25.8 mg/m^3) was studied for markers of genotoxicity using peripheral blood lymphocytes and buccal epithelial cells. Controls were 60 healthy male government workers with no history of wood dust exposure. Statistically significant elevations in DNA damage in peripheral blood lymphocytes were detected in workers using the Comet assay. Increased frequencies of micronuclei and chromosomal aberrations were also detected in the peripheral blood lymphocytes of workers. An increased frequency of micronuclei was also detected in buccal epithelial cells obtained from workers. Micronucleus frequency was increased in both workers and controls who were smokers and consumed alcohol. Serum

levels of superoxide dismutase activity and glutathione peroxidase activity, but not catalase activity, were reduced in the workers (Rekhadevi *et al.*, 2009). [The Working Group noted that the authors of this study could not eliminate a potential effect of exposure to chemical adhesives and wood polish in these workers.]

Çelik & Kanik (2006) studied the frequency of micronuclei and other nuclear alterations in exfoliated buccal mucosal cells from 20 workers occupationally exposed to wood dust and 20 healthy controls. Dust levels in the workplace were 4.7–28.9 mg/m^3. In the controls, the micronucleus frequency was 1.5 ± 1.2% compared to 6.6 ± 1.6% in the workers. Evidence of nuclear injury (karyolysis, karyorhexis) and binucleated cells was also increased in the workers. Smokers in both groups showed increased micronucleus frequency and evidence of nuclear injury. [The Working Group noted that the use of buccal epithelial cells as a surrogate for sinonasal mucosa had not been validated.]

The genotoxicity of six wood dusts and dust from MDF coated with oak was compared in the A549 human lung carcinoma cell line (Bornholdt *et al.*, 2007). As determined by a comet assay, beech, birch, teak, pine, and MDF dusts increased DNA strand breaks 1.2–1.6-fold after 3 hours of exposure. [The Working Group noted that the use of a malignant lung carcinoma cell line as a surrogate for sinonasal epithelial cells is questionable, and that no particulate control group was included.]

No data based on genotoxic assays were available to the Working Group for workers exposed to leather dusts.

4.3.4 Indirect genotoxicity

The most likely mechanism proposed for the carcinogenicity of wood dust is a combination of reduced clearance of large particles from the middle turbinate and ethmoid regions of the sinonasal cavity, leading to mechanical irritation, inflammation, and increased cell proliferation (Llorente *et al.*, 2009). In support of the association between chronic inflammation and sinonasal cancer, Holmila *et al.* (2008) analysed COX-2 and p53 protein expression in 23 cases of adenocarcinoma; 17 were exposed to wood dust and 19 were smokers. Elevated COX-2 expression was found in 13 cases including eight cases who were non-smokers; ten of these cases had a history of wood dust exposure. In 50% of the cases with elevated COX-2 expression, there was elevated p53 protein expression in the same histological pattern as COX-2. COX-2 protein expression was confirmed at the mRNA level.

In a murine model of lung inflammation induced by intranasal instillation of birch or oak dusts two times a week for 3 weeks, oak dust induced more inflammation with an influx of neutrophils and lymphocytes compared with birch dust that elicited an influx of eosinophils (Määttä *et al.*, 2006).

These dusts were also tested for induction of pro-inflammatory mediators from murine RAW 264.7 macrophage cell lines. Birch dust increased the release of the pro-inflammatory cytokines IL-6 and TNF-α, and oak dust caused a smaller release of TNF-α. Birch dust also elicited a stronger chemokine response than oak dust (Määttä *et al.*, 2005).

A panel of six wood dusts and MDF dust was assessed for expression of IL-6 and IL-8 pro-inflammatory cytokines using the human A549 lung carcinoma cell line. Based on expression of IL-8 mRNA, teak dust was more potent than MDF, birch, spruce, or pine dust; with beech and oak dust showing the weakest activity in this assay (Bornholdt *et al.*, 2007).

Human alveolar macrophages obtained from healthy volunteers were exposed to endotoxin-free pine dust for 2 hours. This exposure induced a dose-dependent release of the pro-inflammatory mediators, TNF-α and MIP-2, that was associated with increased production of reactive oxygen species (Long *et al.*, 2004).

No experimental data were available to the Working Group on the release of inflammatory mediators from animals or cell cultures following exposure to leather dusts.

Overall, these experimental studies provide evidence that wood dust from a variety of hardwoods and softwoods can elicit the release of pro-inflammatory mediators after short-term exposures, and suggest a possible association between inflammation and the development of cancer.

In summary, the mechanism responsible for the carcinogenicity of wood or leather dusts is unknown as concluded previously by IARC (1995). In 2000, the Health Council of the Netherlands concluded that wood dust cannot be classified as a non-genotoxic carcinogen or as a direct or indirect genotoxic carcinogen due to insufficient mechanistic data (Feron *et al.*, 2001).

4.4 Other risk factors for sinonasal and nasopharyngeal cancers

The most important exposures associated with the development of sinonasal cancers are occupational exposures in furniture and woodworking industries, leather and shoe manufacturing, and in nickel workers (Table 4.1; IARC, 2012b).

Exposures to other agents classifed by IARC as *carcinogenic to humans (Group 1)* have also been associated with cancers of the nasal cavity and paranasal sinuses (Table 4.1).

Other occupations that have been suggested to be linked with the development of sinonasal cancers include agricultural workers, workers in food manufacturing and preserving, and workers in the textile industry, and in the manufacturing of rubber and plastic products (Leclerc *et al.*, 1997; Luce *et al.*, 2002).

Nasopharyngeal cancers occurring in low-risk populations, including Europe and the US, peak in adolescents and young adults and are associated with Epstein-Barr virus (EBV) infection. The highest risk populations are in the Cantonese region of Southern China and Hong Kong Special Administrative Region, followed by Taiwan, China, the Arctic region, Southeastern Asia, and North Africa. In these high-risk populations, peak incidence is at 50–59 years and the most important risk factors are dietary in association with EBV infection (Yu & Yuan, 2002; IARC, 2012a).

Table 4.2 Other risk factors for nasopharyngeal cancer[a]

Exposure	Reference
Chlorophenol	Zhu *et al.*, (2002), IARC (1999)
Epstein-Barr virus (EBV)	IARC (1997, 2012a)
Ingestion of salted fish and preserved foods during childhood	IARC (2002, 2012c)
Formaldehyde	IARC (1995, 2012d)
Mustard gas	IARC (1987, 2012d)
Tobacco smoking	IARC (2002, 2012c)

[a] All classifed as Group 1 carcinogens except for chlorophenol (2B)

Tobacco smoking is a risk factor for both sinonasal cancer ('t Mannetje *et al.*, 1999; IARC, 2002) and nasopharyngeal cancer, in addition to occupational exposure to formaldehyde or mustard gas (Table 4.2). Squamous cell carcinomas in the nasopharynx have also been linked with exposure to a wood preservative, chlorophenol (Table 4.2; IARC, 1999; Zhu *et al.*, 2002).

It is worth noting that EBV infects almost everyone worldwide but the infection is usually kept dormant by the immune system. Exposure to agents that deregulate the immune system may potentially activate this oncogenic virus (IARC, 2012a).

No published reports were available to the Working Group on genetic susceptibility to development of sinonasal cancers or nasopharyngeal carcinoma associated with exposure to wood or leather dusts.

4.5 Synthesis

Potential mechanisms responsible for the carcinogenicity of wood dust include tissue injury induced by the deposition of wood dust particles in the sinonasal region, impaired ciliary clearance, direct genotoxicity and indirect genotoxicity secondary to chronic inflammation. Wood or leather dusts may also act as carrier for other genotoxic agents (e.g. chromate). There is weak evidence for these mechanisms in cellular assays, short-term animal assays, or assays for genotoxicity using peripheral blood cells or buccal epithelial cells obtained from workers exposed to wood dust.

Workers exposed to wood or leather dusts have increased frequencies of metaplasia and hyperplasia in nasal epithelial biopsies, although these alterations are not considered to be precursor lesions of neoplasia at this organ site. In one study, leather workers also showed increased evidence of dysplasia in nasal biopsies. No mechanistic data were available to the Working Group for leather dust exposure.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of wood dust. Wood dust causes cancer of the nasal cavity and paranasal sinuses and of the nasopharynx.

There is *inadequate evidence* in experimental animals for the carcinogenicity of wood dust.

Wood dust is *carcinogenic to humans (Group 1).*

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LIST OF ABBREVIATIONS

8-h TWA	Eight-hour TWA
8-OH-dG	8-hydroxydeoxyguanine
AAS	atomic absorption spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists
AG-AAS	Arsine generation atomic absorption spectrometry
AS3MT	arsenic +3 oxidation state methyltransferase
ASA Register	Finnish Register of Workers Exposed to Carcinogens
As–GSH	arsenic–glutathione
BALF	bronchoalveolar lavage fluid
CARET	Beta-Carotene and Retinol Efficacy Trial
CAREX	CARcinogen EXposure
CAS	Chemical Abstracts Service
CBD	chronic beryllium disease
DMAs	dimethylated arsenic species
DMAV	dimethylarsinic acid
DMBA	7,12-dimethylbenz[α]anthracene
DMMTAV	Dimethylthioarsinic acid
DQ12	uncoated quartz
DSMA, or cacodylic acid	disodium methanearsonate
DWA	Daily weighted average
EBV	Epstein-Barr virus
ECVAM	Centre for the Validation of Alternative Methods
EDAX	energy dispersive analysis of X-rays
ET-AAS	electrothermal atomic absorption spectroscopy
F344	Fisher 344
FBs	Ferruginous bodies
Fpg	formamidopyrimidine-DNA-glycosylase
G6PD	glucose 6-phosphate dehydrogenase
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GC-ECD	gas chromatography-electron capture detection
GF-AAS	graphite furnace atomic absorption spectrometry
GSD	geometric standard deviation
GSH	glutathione
HOBr	hypobromous acid
HOC1	hypochlorous acid
hOGG1	human 8-oxoguanine-DNA-glycosylase
HPV	human papillomavirus

ICP-AES	inductively coupled plasma atomic emission spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
IMA	International Mineralogical Association
IMIS	Integrated Management Information System
ITAC	intestinal-type sinonasal adenocarcinoma
JEM	job–exposure matrix
LEV	local exhaust ventilation
MBDs	methyl-CpG binding domains
MDF	medium-density fibreboard
MGMT	O6-methylguanine-DNA methyltransferase
MIG/MAG-method	Metal Inert Gas-Metal Active Gas
MLHT	malignant lymphomas of the histiocytic type
MMAD	mass median aerodynamic diameter
MMAs	Monomethylated arsenic species
MMAV	monomethylarsonic acid
MnTBAP	manganese(III)meso-tetrakis(4-benzoic acid)porphyrin
MSHA	Mine Safety and Health Administration
MSMA	monosodium methanearsonate
NDEA	N-nitrosodiethylamine
NHANES III	Third National Health and Nutrition Examination Survey
Ni–Cd	nickel–cadmium
NIOSH	National Institute of Occupational Safety and Health
NOES	National Occupation Exposure Survey
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAHs	polyaromatic hydrocarbons
PARP	poly ADP-ribose polymerase
PCP	pentachlorophenol
PD-1	programmed death-1
PMNs	polymorphonuclear leukocytes
PMR	proportionate mortality ratio
RCF-1	refractory ceramic fibres
REL	recommended exposure limit
RLE-6TN	type II lung epithelial cells
RR	relative risk
SHE	Syrian hamster embryo
SiO4	silicate tetrahedron
SIR	standardized incidence ratio
SMR	Standard Mortality Ratio
SV40	simian virus 40
TEM	transmission electron microscopy
TPA	12-O-tetradecanoyl phorbol-13-acetate
TWA	Time-weighted average
UV	ultraviolet
UVR	ultraviolet radiation
XPA	xeroderma pigmentosum group A
XRCC1	X-ray complementing group 1 gene
Zn	zinc

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Volume 100 of the *IARC Monographs*, A Review of Human Carcinogens, covers all agents previously classified by IARC as *carcinogenic to humans (Group 1)* and was developed by six separate Working Groups: Pharmaceuticals; Biological Agents; Arsenic, Metals, Fibres, and Dusts; Radiation; Personal Habits and Indoor Combustions; Chemical Agents and Related Occupations.

This Volume 100C covers Arsenic, Metals, Fibres, and Dusts, specifically Arsenic and Arsenic Compounds, Beryllium and Beryllium Compounds, Cadmium and Cadmium Compounds, Chromium (VI) Compounds, Nickel and Nickel Compounds, Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite and Anthophyllite), Erionite, Leather Dust, Silica Dust, Crystalline, in the form of Quartz or Cristobalite, and Wood Dust.

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the agent's toxicokinetics, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results are printed in Volume 100, and more extensive tables that include all studies appear on the *Monographs* programme website (http://monographs.iarc.fr).

It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.